

ASYMMETRIC INDUCTION IN THE 1,7 RING CLOSURE OF
DIENE-CONJUGATED DIAZO-COMPOUNDS

by

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Abstract

This thesis describes an investigation into the asymmetric induction found in the electrocyclisation of diazo-compounds having $\alpha, \beta; \gamma, \delta$ -unsaturation.

It is thought that the reaction involves two steps, first, an 8π electron 1,7-electrocyclisation in which orbital overlap at the termini of the π system is achieved via a helical transition state; and second, an intramolecular suprafacial sigmatropic [1,5] hydrogen shift.

The results reported here are concerned with the effect of the presence of a chiral substituent at the terminal trans position of the conjugated system in the first step. The second step transfers the chirality stereospecifically, creating a new chiral centre. By measurement of the diastereomeric ratio and a determination of the relative configuration of the two chiral centres, the face selectivity of the chosen chiral groups were assessed.

When the medium sized group in the chiral substituent was an alkoxy or hydroxy group, cyclisation at the more hindered face of the alkene in its lowest energy conformation predominated. Polar repulsion effects are thought to be the factors controlling the conformation of the chiral group.

When the medium sized group was an alkyl group or an alkoxide ion, the less hindered face was preferred. In the former, steric repulsion effects are believed to dominate the conformation. While, in the latter, polar attraction between the cation and the nitrogen of the diazo-group may stabilize the preferred conformation.

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INTRODUCTION

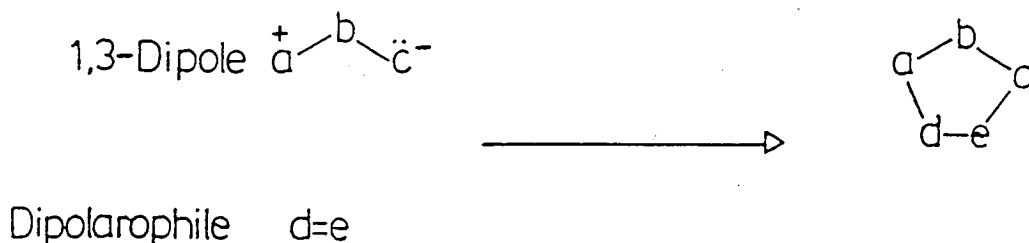
1) 1,3-DIPOLES

1.1) Structure

Although some classes of 1,3-dipole have been known for over a hundred years, it was not until the 1960's that the classification of 1,3-dipoles by Huisgen,¹ led to a more intense study of the subject.

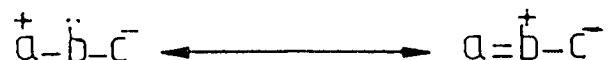
A 1,3-dipole may be defined^{2,3} as a system a-b-c in which a has an electron sextet, i.e. an incomplete valence shell, and carries a formal positive charge; and c is a negatively charged centre having an unshared electron pair.

1,3-Dipoles react readily with most multiple bond systems, the dipolarophile, to give a five-membered cyclic product, via a [3 + 2 \longrightarrow 5] cycloaddition, in which σ bonds are formed at the a and c termini and the formal charges are lost.



Dipoles in which the positive centre a is an electron-deficient carbon, nitrogen or oxygen are generally not stable enough for long-lived existence.

However stabilisation is possible by donation of an unshared pair of electrons at atom b, as shown below.



An all octet structure is thus attained in which b becomes the site of formal positive charge. By varying the atoms a, b and c it is possible to construct a series of 1,3-dipoles, as shown in Table 1.

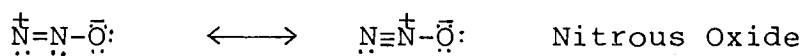
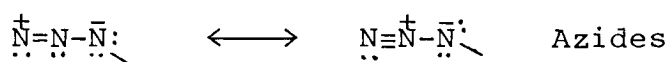
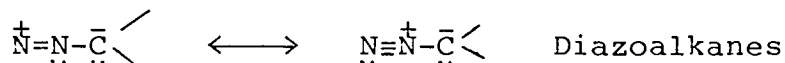
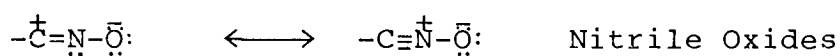
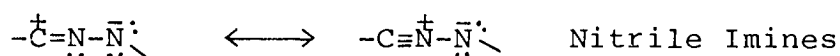
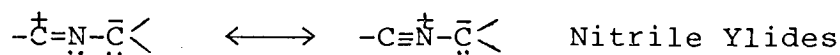
All 1,3-dipoles contain an allyl anion type π system, i.e. four electrons in three parallel atomic p orbitals, but an element of variation is provided by the incorporation of an additional π bond in the plane perpendicular to the allyl anion molecular orbital in 1,3-dipoles of the propargyl-allenyl type. Usually, the occurrence of this extra π bond makes 1,3-dipoles of the propargyl-allenyl type linear, whereas 1,3-dipoles of the allyl type are bent.

Propargyl-allenyl type 1,3-dipoles have nitrogen as the central atom b, since this is the only element which can supply an unshared electron pair while in a neutral trivalent state. Allyl type 1,3-dipoles can have either nitrogen or oxygen as the central atom. In addition, there are also a number of systems with no octet stabilisation which will not be discussed here as they are not relevant to this thesis.

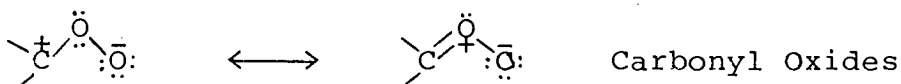
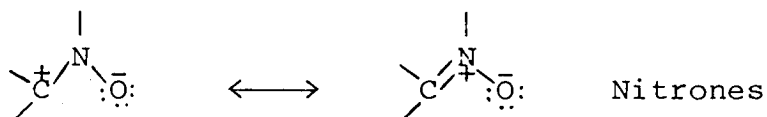
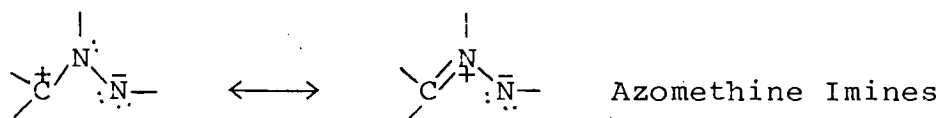
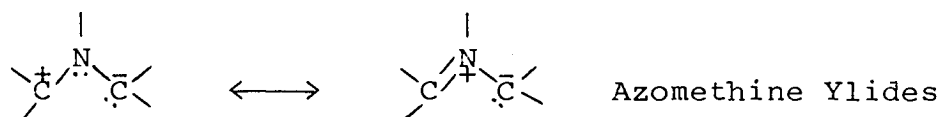
Table 1. 1,3-Dipoles with octet stabilisation

(only two of the contributing canonical forms are shown for each dipole)

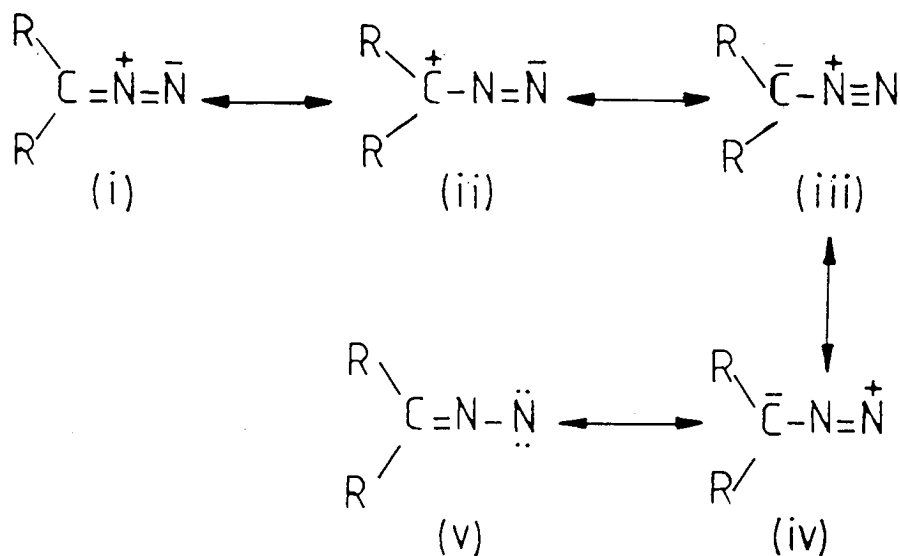
a) 1,3-Dipoles of the propargyl-allenyl type



b) 1,3-Dipoles of the allyl type



1,3-Dipoles are best represented by resonance structures, for example (i)-(v) are the canonical forms for a diazoalkane (Scheme 1).



Scheme 1

The all octet structures (i) and (iii) are the main contributors to the stability of these compounds. The term 1,3-dipole which best describes the mode of reaction, derives from the sextet structures (ii) and (iv) but these, and the nitrenic structure (v), give much less significant contributions.

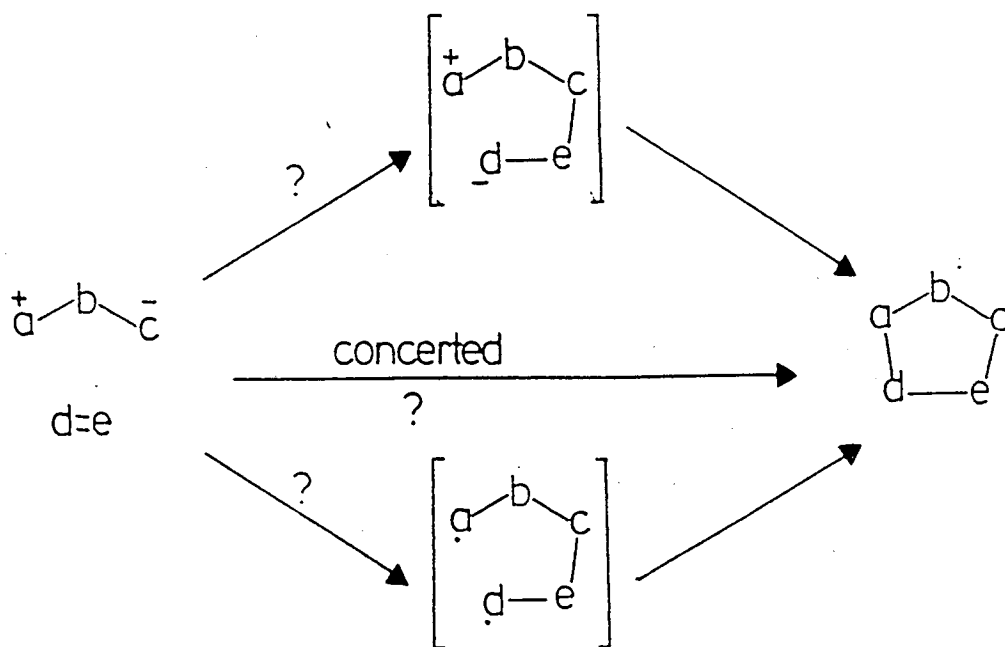
Cycloadditions of 1,3-dipoles can be of two types, either "inter-" or "intra-" molecular and will now be discussed in more detail under these headings.

1.2) Intermolecular 1,3-Dipolar Cycloaddition

The general features of mechanism and patterns of reactivities and selectivities in 1,3-dipolar cycloadditions were established experimentally by Huisgen et al^{3,4}

Common mechanistic features include; (i) the reactions are not markedly influenced as to rate or stereochemistry by solvent polarity, (ii) stereospecific cis addition producing 5-membered rings in which the olefin stereochemistry is retained, (iii) the reactions show low enthalpies of activation, (consistent with a concerted mechanism) and, (iv) reaction rates are markedly increased by conjugation of the dipolarophile, but reduced by the steric effects of all types of dipolarophile substituent.

The mechanism of 1,3-dipolar cycloadditions had been a topic of lively debate between the proposers of a concerted or a two-step mechanism (Scheme 2).



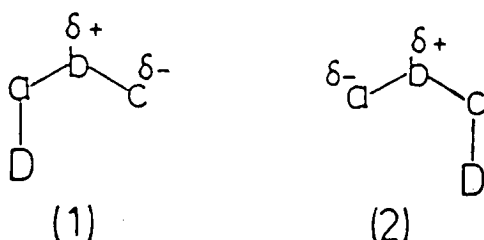
Scheme 2

Huisgen's^{2,3} original proposal of a concerted [3+2] mechanism involving a cyclic transition state but no discrete intermediate was later backed up by the Woodward-Hoffmann⁵ rules which showed that this mechanism was allowed on the basis of conservation of orbital symmetry. A later proposal by Firestone⁶ involves a two-step mechanism in which the formation of a discrete spin paired diradical is the rate determining step. One major problem for this mechanism is the fact that the stereochemistry of the addition is cis but Firestone explained this in terms of ring closure being energetically more favoured than bond rotation in the diradical. Firestone also suggested that the effects of conjugation and solvent polarity could be best explained by the diradical mechanism. He suggested that the orientation could be predicted by considering the four possible diradical intermediates, taking into account steric, kinetic and σ bond energy factors. The reply by Huisgen⁴, while acknowledging that orientation remained an unsolved problem, strongly defended the concerted mechanism on the basis of stereochemical, energetic and electronic grounds. Huisgen also asserted that the effects of conjugation and solvent polarity could be explained by synchronous, but not simultaneous, bond formation in the transition state.

In 1972 Firestone⁷ again presented the diradical mechanism, his argument in this case being based entirely on the problem of orientation in 1,3-dipolar cycloadditions.

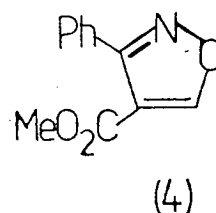
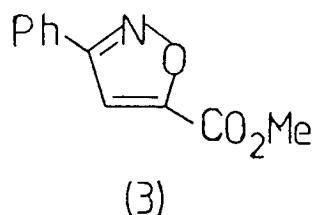
Firestone first addressed himself to the predominant unidirectionality of orientation exhibited by most 1,3-dipoles

towards both electron-rich and electron-poor dipolarophiles which conflicted with the concerted mechanism but agreed with the diradical intermediate. This was based on the consideration of the 1,3-dipole and diradicals as Linnett structures⁸ since the more conventional Lewis structures did not take into account the stabilisation of radical centres adjacent to heteroatoms by partial bonding.



The Linnett structures (1) and (2) have partial formal charges and the bond energy is the same for both structures. The more stable diradical will be that in which the more electronegative atom bears the formal negative charge. This will then be the most favoured diradical, and so orientation, irrespective of whether the dipolarophile (D) is electron donating or withdrawing, and hence the unidirectionality of the orientation regardless of the nature of the dipolarophile.

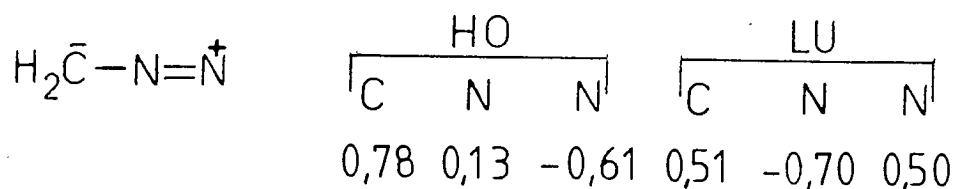
The second factor favouring the diradical mechanism was steric, although previously this had been the foundation of orientation according to the concerted mechanism.^{2,3} Thus, the regioselectivity favouring the formation of (3) over (4) of 72% had been rationalised as being due to steric interaction in the transition state.



However, when the phenyl ring was replaced by hydrogen⁹, the regioselectivity of (3) over (4) increased to 84% instead of decreasing. While substituting a mesityl group for phenyl the regioselectivity was inverted to 28%. These facts could not be accounted for by the concerted mechanism so Firestone concluded that the evidence favoured the diradical mechanism.

In 1973, Houk and co-workers^{10,11} developed a new and powerful method which rationalised substituent effects on rates, regioselectivity and periselectivity of concerted 1,3-dipolar cycloadditions. This was based on perturbation theory and utilised relative energies and co-efficients of the frontier orbitals of the interacting 1,3-dipoles and dipolarphiles which were calculated by CNDO/2. The calculated orbital energies were then adjusted with the help of known ionisation potentials, electron affinities and $\pi - \pi^*$ transitions in alkenes. Fukui¹² had earlier postulated that the reactions take place in the direction of maximum frontier orbital overlap, i.e. between the highest occupied (HO) and lowest unoccupied (LU) orbitals.

For diazomethane (5) the absolute values for the frontier orbital coefficients (CNDO/2) were as follows²³:-



It can be seen from these calculations that the two termini have different coefficients (as do the termini of unsymmetrical dipolarophiles), the HOMO being heavily localised on the CH_2 terminus. The sizes of these coefficients may be represented pictorially as lobes. Thus, when 1,3-dipolar cycloaddition occurs, two possible transition states, (5) and (6), may be envisaged (Figure 1) depending upon the relative orientation of the dipole and dipolarophile.

The preferred transition state will always be that which results in the union of the two centres of highest frontier orbital density and the union of the two centres of lowest density.

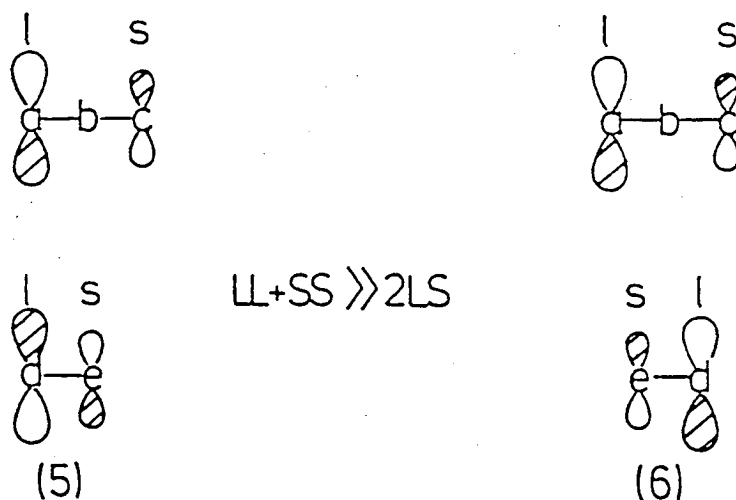


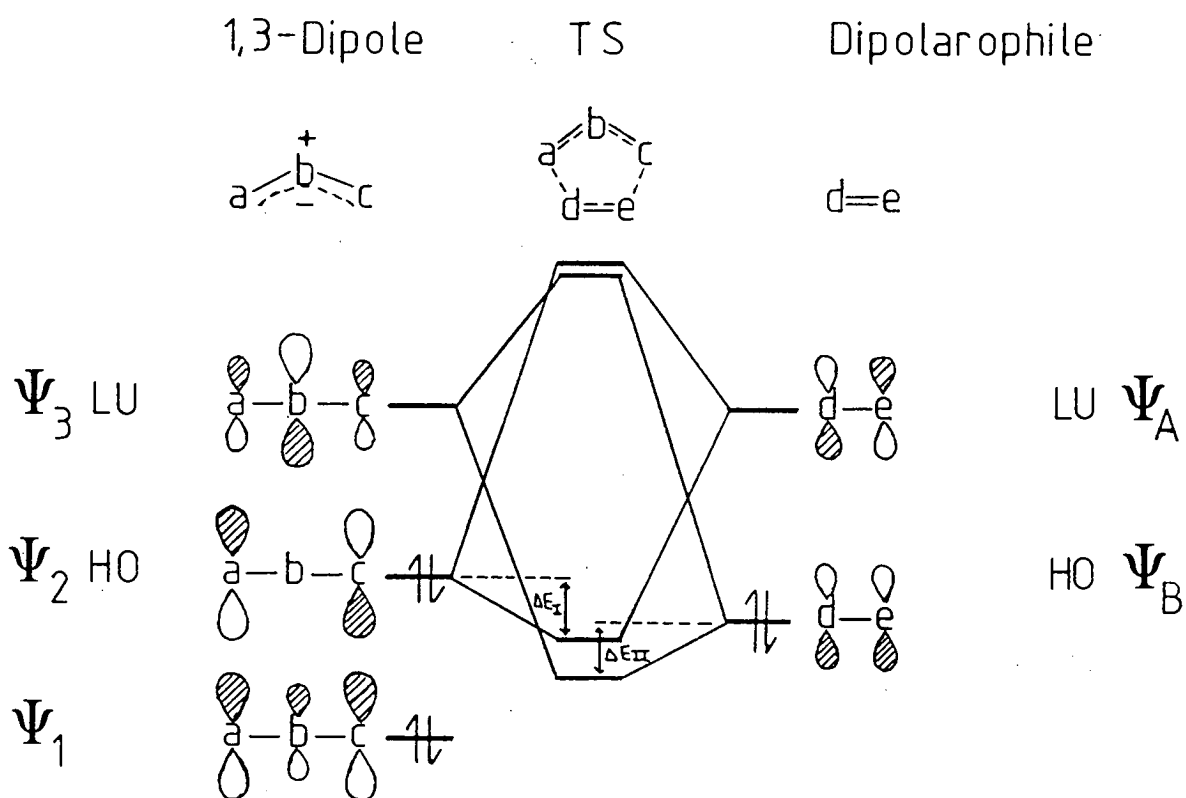
Figure 1

Since the relative energies and orbital coefficients of the HO and LU orbitals are strongly affected by the substituents, and are the chief factors in determining the mode of regioselectivity and rates of reaction, Houk was able to achieve a complete rationalisation of the observed results in terms of substituent effects; except for nitrile ylides for which CNDO2 with no geometry optimisation, gave inaccurate coefficients for the dipole (later corrected by more refined calculations). A cycloaddition controlled by a strong interaction (5) would also lead to unequal extents of bond formation in the transition state, bond a-d being more fully developed than bond c-e. Huisgen¹⁴ has used the molecular orbital perturbation treatment as extra support for the concerted mechanism.

Firestone, however, retains his convictions and he has argued¹⁵ that perturbation molecular orbital theory bases its predictions on ground state interactions between reactants and maintains that calculations of ground state orbitals are meaningless when the transition state lies more than 30-70 KJ/mole above the ground state in energy.

In recent years, there has been increasing activity in the search for two step 1,3-dipolar cycloadditions.

In 1971, Sustmann successfully explained reactivity sequences in concerted cycloadditions by applying molecular orbital perturbation theory^{16,17}. In Figure 2, the frontier π —MOs of the 1,3-dipole and those of an ethylenic dipolarophile are depicted.



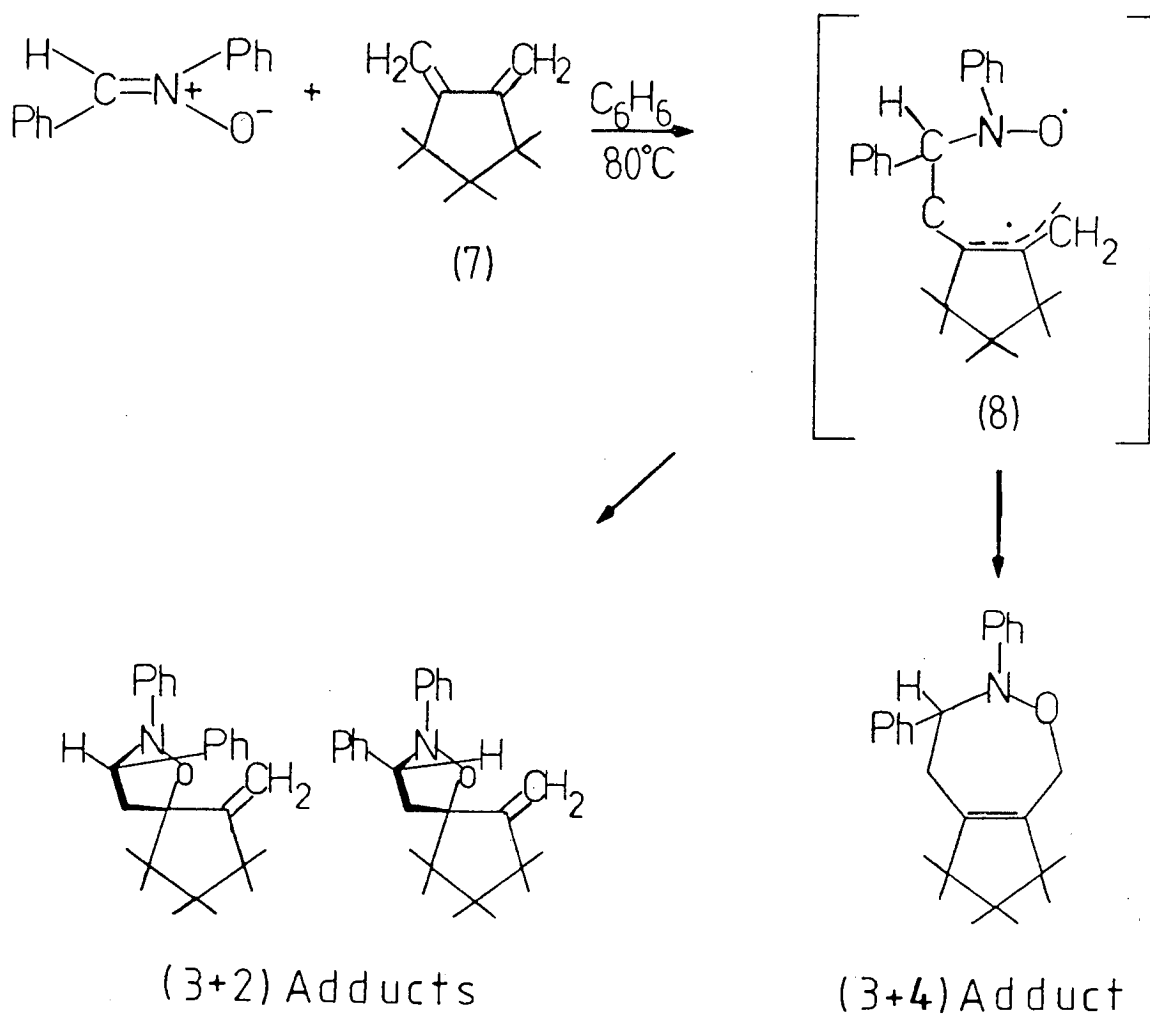
$$E_I = E_{\Psi_2} - E_{\Psi_A} = \text{HO (1,3-Dipole)} - \text{LU (Dipolarophile)}$$

$$E_{II} = E_{\Psi_B} - E_{\Psi_3} = \text{HO (Dipolarophile)} - \text{LU (1,3-Dipole)}$$

Figure 2

The diagram reflects the two-directional electron flow during the concerted cycloaddition; from HO(1,3-dipole) to LU(dipolarophile) and back by the second interaction. If the energy distances in the two interacting FMO pairs are large and of the same magnitude then the sum of the two energy gains, $\Delta E_I + \Delta E_{II}$ is small. A diradical pathway may therefore compete with a concerted pathway in the presence of radical stabilising substituents.

The first example of this pathway (Scheme 3) was recently uncovered by Mayer and Baran¹⁸. The sterically hindered 1,3-diene (7) combined with diphenylnitrone to give 32% of diastereoisomeric (3+2) adducts and 18% of a (3+4) adduct. Orbital symmetry forbids a concerted pathway leading to the 7-membered ring. The intermediate (8) looks attractive, stabilised as a nitroxyl radical and an allyl radical. 1,5 and 1,7 recombination could give rise to the isolated products.



Scheme 3

A mechanism via a zwitterionic intermediate will compete in another limiting situation. In Figure 3, ΔE_{π} is smaller than ΔE_I , because LU(1,3-dipole) and HO(dipolarophile) are more widely separated in their energies than the second frontier orbital pair. If the π -MO energies of the 1,3-dipole are further lifted and those of the dipolarophile lowered, ΔE_{π} should become negligibly small. The circular flow of electrons would then become unidirectional, from HO(1,3-dipole) to LU(dipolarophile).

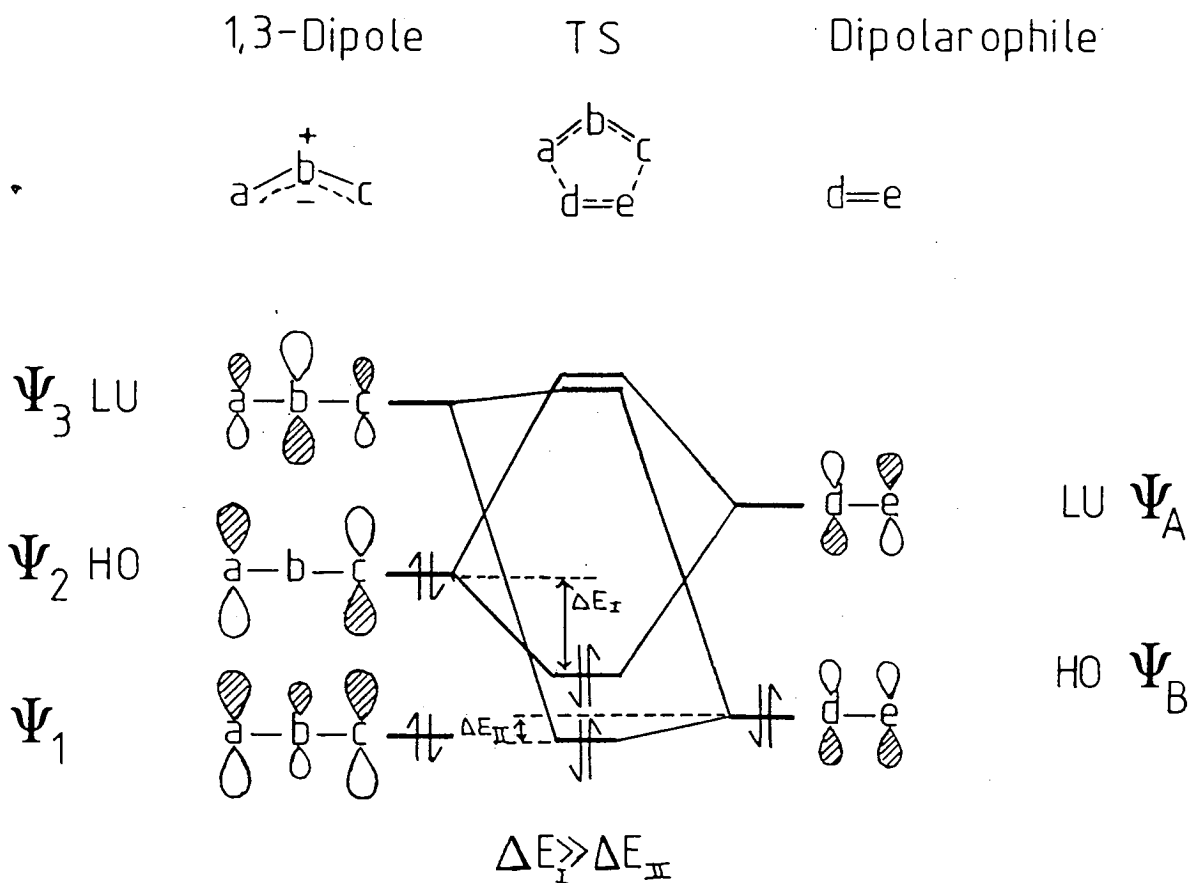
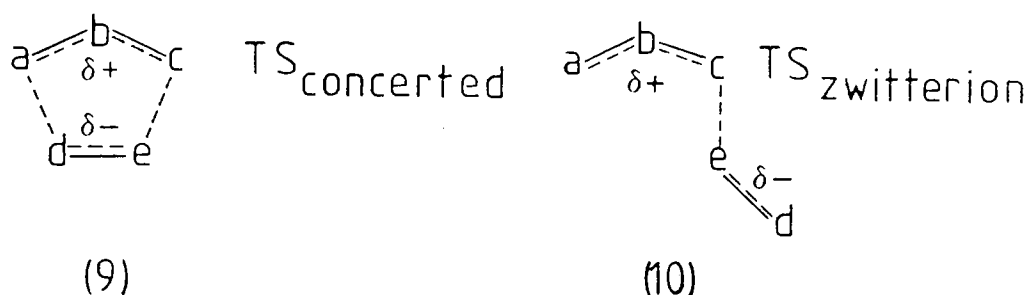


Figure 3

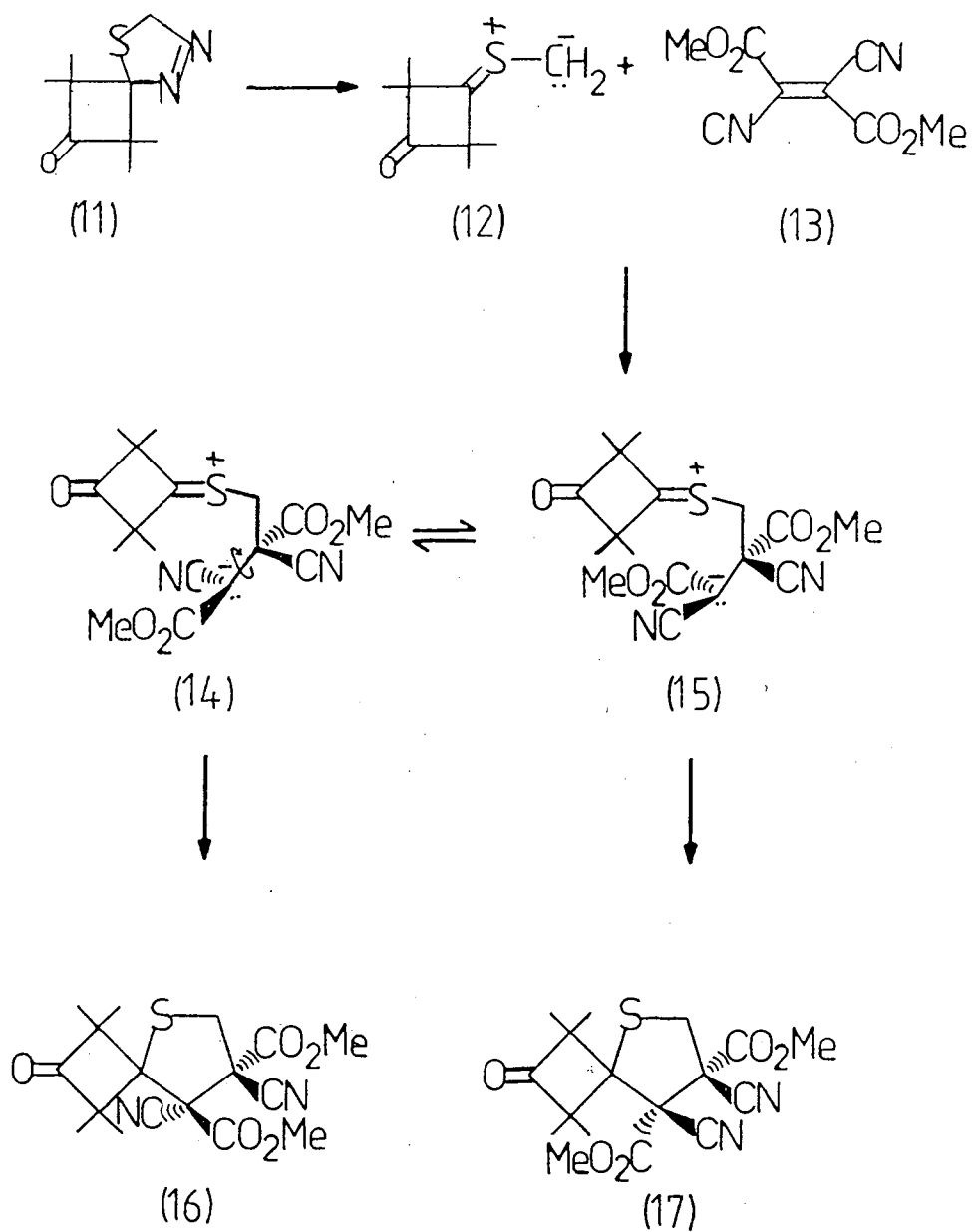
In transition state (9) both terminal centres of the delocalized allylic system participate in the unidirectional flow. To favour zwitterionic transition state (10) either the atomic orbital terminus a must be very small compared with that at terminus c, or strong steric encumbrance at a must impair the a-d interaction.



Thus, the emergence of a zwitterionic intermediate requires a 1,3-dipole with high π -MO's i.e. a nucleophilic one and a structural symmetry disturbed by substitution. The dipolarophile must be an electrophilic ethylene derivative with very low π -MO's.

Huisgen¹⁹ found that aliphatic thiocarbonyl ylides, together with an ethylene derivative bearing four electron attracting substituents offered a reactant pair with extremely different MO energies.

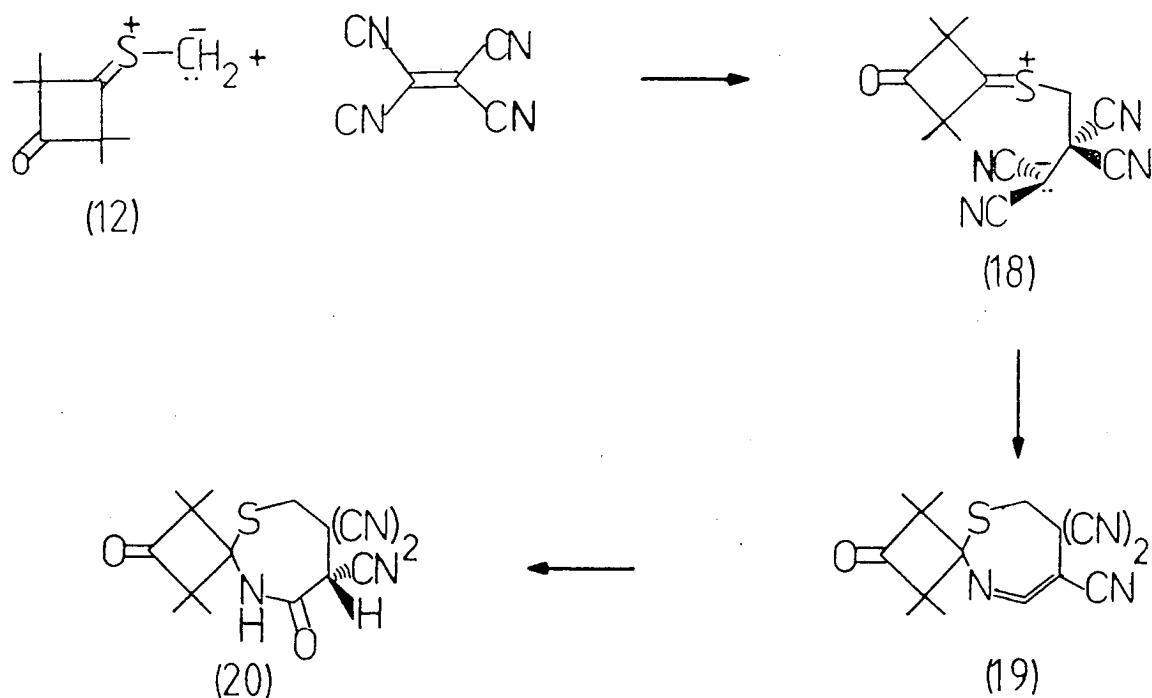
Crystalline spiro-1,3,4-thiodiazoline (11) eliminates nitrogen in THF at 40°C to give the thiocarbonyl ylide (12). This reacts in situ with dipolarophiles such as dimethyl-2,3-dicyanofumarate (13) which has lower MO energies than ethene to give cycloadducts (16) and (17) in good yield (Scheme 4).



Scheme 4

A 52:48 mixture of diastereoisomeric cycloadducts (16) and (17) was isolated. The nonstereospecificity implies a zwitterionic intermediate capable of rotation (14) to (15).

Further work²⁰ intercepted the intermediate (12) using tetracyanoethylene in moist THF to give the spiro structure (20) (Scheme 5). Two intermediates, (18) and (19) explain the formation of the product (20). More recently a cyclic ketenimine intermediate has been isolated and the structure determined by x-ray crystallography. Stabilisation was achieved by CF_3 groups.



Scheme 5

In both the above examples, the bond system of the thiocarbonyl ylide (12) is planar, and the dipolarophile approaches from frontside or rearside. However, the geminal dimethyl groups of (12) sterically hinder the approach of the tetrasubstituted ethylene. But, formation of the zwitterion (14) or (18) is less hindered because the dipolarophile first anchors at the methylene terminus. This agrees with Sustmann's earlier predictions.

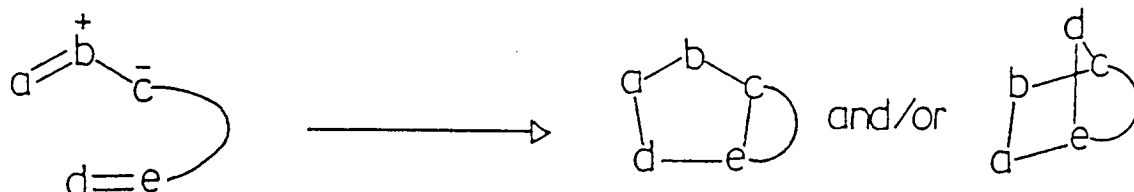
Following these results Huisgen has forced the question - Is it conceivable that all 1,3-dipolar cycloadditions do take the two step course and that λ ^{the} rotation/ cycloaddition ^{ratio} is too small as a rule to allow detection of the nonstereospecific portion? Bihlmaier²¹ has studied the addition of diazomethane to methyl tiglate and a retention of >99.997% was found for the stereospecific cycloadduct. Houk, Firestone and co workers²² tested the addition of 4-nitrobenzonitrile oxide to cis and trans-dideuterioethylene; >98% retention was observed. One can conclude from all this work that normal stereospecific 1,3-dipolar cycloadditions follow a fundamentally different mechanism involving no intermediates¹⁹.

Despite the controversy over mechanism, the usefulness of 1,3-dipolar cycloadditions to form five-membered heterocycles is unquestionable. Numerous papers and reviews²³ have dealt with 1,3-dipolar cycloadditions to alkenes³, alkynes²⁴ and other double bonded functional groups²⁵.

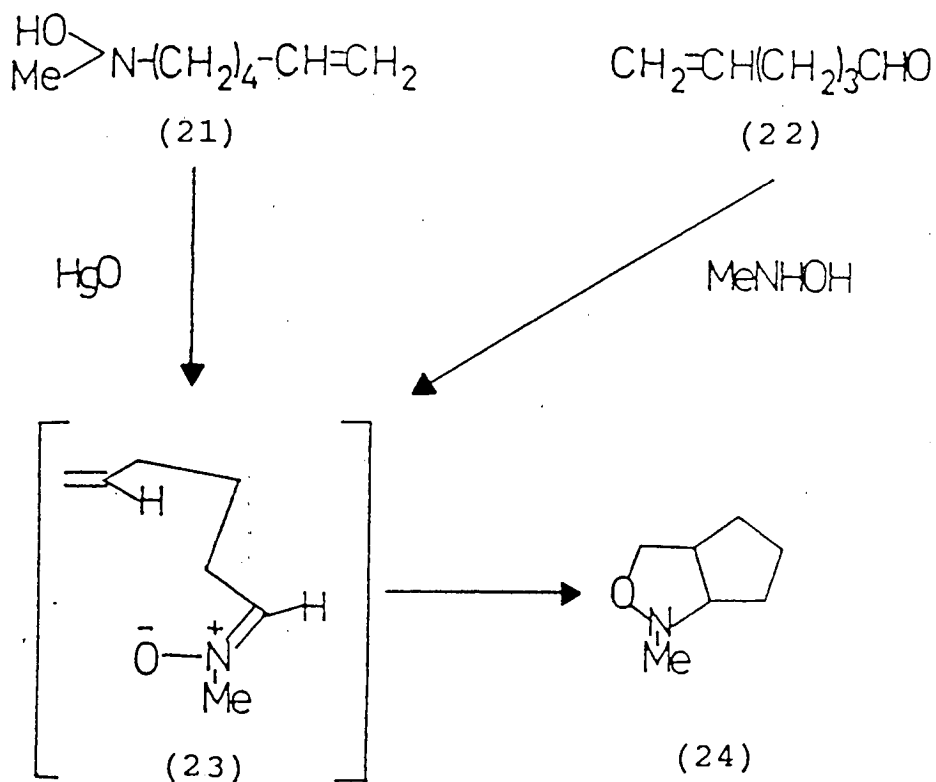
1.3) Intramolecular 1,3-Dipolar Cycloadditions

Despite the extensive literature dealing with bimolecular 1,3-dipolar cycloadditions, intramolecular examples have only recently started to receive more widespread attention.

In an intramolecular cycloaddition reaction, both the dipole and the dipolarophile are contained in the same molecule. The cyclisation occurs via a [3+2→5] mechanism to form a fused five-membered ring heterocycle.



The first example of an intramolecular 1,3-dipolar cycloaddition was reported by LeBel and Whang²⁶ in 1959. The nitron (23), prepared from either oxidation of an N-alkenylhydroxylamine (21) by mercuric oxide or condensation of an unsaturated aldehyde (22) with N-methylhydroxylamine gave a fused bicyclic isoxazolidine (24) (Scheme 6).



Scheme 6

Reviews^{23,27} on intramolecular cycloaddition reactions have been published and numerous papers^{describe} the use of this reaction in the synthesis of natural products.

Nitrones, diazoalkanes, azides, azomethine imines, nitrile imines, nitrile ylides, carbonyl oxides and nitrile oxides have all been shown to undergo intramolecular cycloaddition²³.

1.4) Electrocyclic Reactions

Another possible intramolecular mode of reaction for 1,3-dipoles is an electrocyclic reaction²⁸. In this case, the 1,3-dipole must be in conjugation with the dipolarophile. An

electrocyclisation reaction is defined²⁹ as one in which an unsaturated system undergoes a ring closure in a process that can be regarded as a cyclic electron shift, the net result being the conversion of a π bond into a σ bond. In principle electrocyclisation is a reversible process and cyclic systems can open by electrocyclic ring opening to give polyenes (Figure 4), this process taking place via the same energy profile as the ring closure.

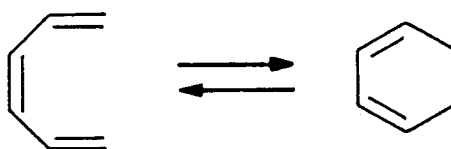


Figure 4

Electrocyclisation reactions can occur in both neutral and charged species of various ring sizes^{29,30}. Electrocyclic processes belong to the class of one-step pericyclic reactions which conform to the principle of conservation of orbital symmetry. The steric course of these processes can be predicted by inspection of the symmetry of the highest occupied molecular orbital.

1,3-Dipolar electrocyclic reactions fall into three main classes; 1,3-retro-electrocyclisation (4π), 1,5-electrocyclisation (6π) and 1,7-electrocyclisations (8π).

1,3-Retro-electrocyclisations are of great use in the generation of 1,3-dipoles, especially nitrile ylides via the photolysis of azirines, azeomethine ylides by the thermolysis of aziridines^{31,32}, azomethine imines by the thermolysis of diaziridines^{33,34} and carbonyl ylides by the thermolysis of

photolysis of oxiranes^{35,36} (Figure 5).

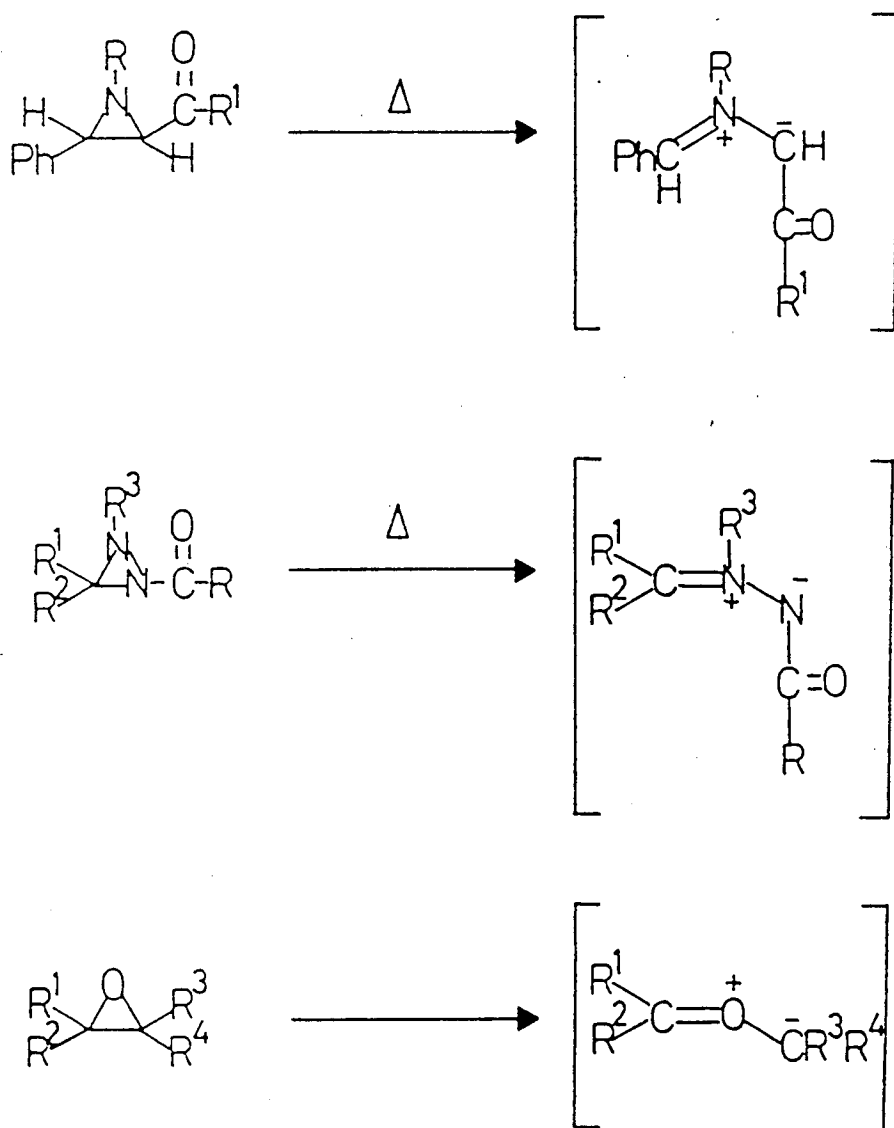
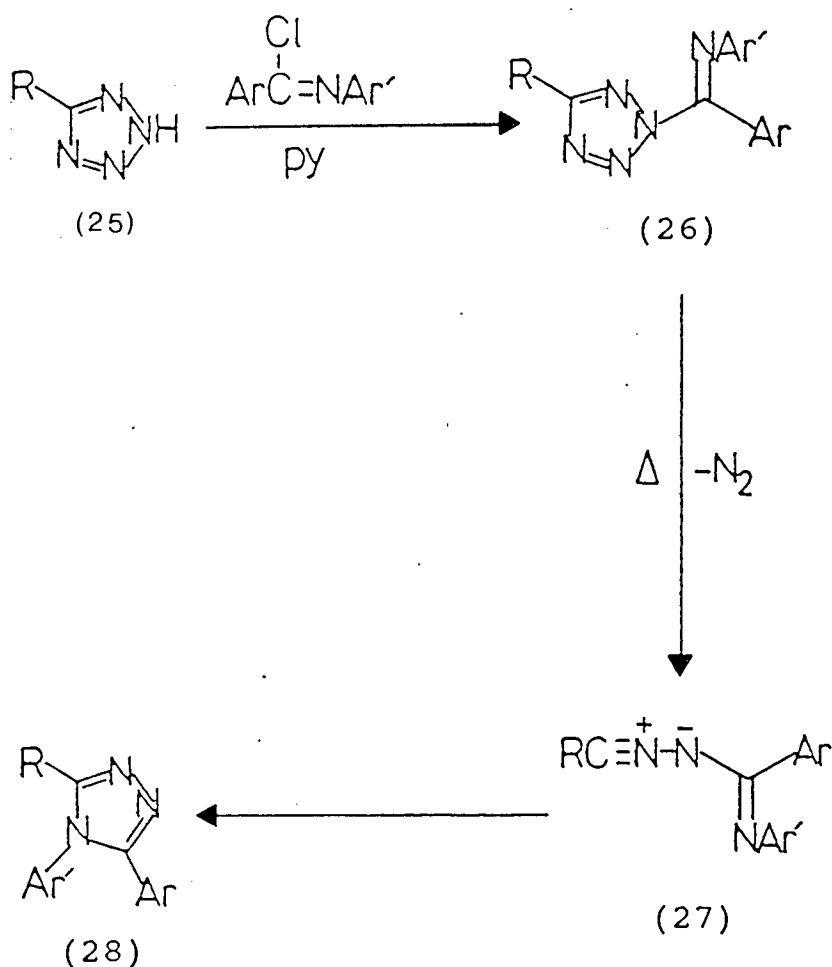


Figure 5

1,3-Dipoles of both the propargyl-allenyl and allyl type when conjugated with a double bond are capable of 1,5-electrocyclisations (6π) to form charge free five-membered rings, for example, 5-alkyl- or 5-aryltetrazoles (25) react with diarylimidoyl chlorides in pyridine to afford 1,3,4-triazoles (28) in high yields³⁷. This reaction proceeds via the intermediate tetrazoles (26) which lose nitrogen to

give iminonitrile imines (27), the 1,5-electrocyclisation of which gives the observed 1,3,4-triazoles (28).



Scheme 7

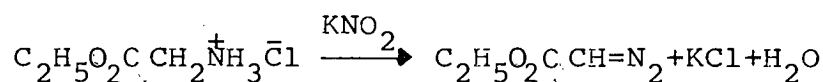
The conjugated double bond in these systems has included $C=C$, $C=O$, $C=N$ and $C=S$.

1,5-Electrocyclisation of 1,3-dipoles has been used with great success in the synthesis of many monocyclic and fused unsaturated, aromatic and heteroaromatic ring systems and has been the subject of major reviews;^{30,38}

The 1,7-electrocyclisation of diazoalkanes will be treated in greater detail in the next chapter of this thesis.

2) DIAZOALKANES2.1) Properties and Synthesis of Diazoalkanes

Diazoalkanes are 1,3-dipolar species best represented as a resonance hybrid, comprising linear structures with opposing dipoles (Scheme 1, page 4). The first known diazoalkane was diazoacetic ester prepared by Curtius³⁹ in 1883 by treatment of glycine ethyl ester hydrochloride with potassium nitrite.



The simplest diazoalkane, diazomethane (CH_2N_2) is a highly toxic, yellow gas, explosive at room temperature. It has been shown to have a linear, planar structure by electron diffraction⁴⁰ and microwave spectroscopy⁴¹. The resonance hybrid structure is supported by bond length ($\text{C} \xrightarrow{1.300} \text{N} \xrightarrow{1.139} \text{N}$) and ^{13}C n.m.r. spectroscopy⁴² shows that the carbon atom has a high electron density (δ 23.1), showing a large contribution from structures with a negative charge on carbon.

The thermal stability of higher homologues depends markedly on the nature of substituents. Conjugating substituents, regardless of whether they are electron releasing or electron withdrawing, increase stability. Non conjugating electron withdrawing substituents increase stability as they favour a resonance hybrid structure having a formal carbanion ($\text{R}_2\text{C}^--\text{N}_2^+$), whereas non-conjugating electron releasing substituents decrease stability as they favour a

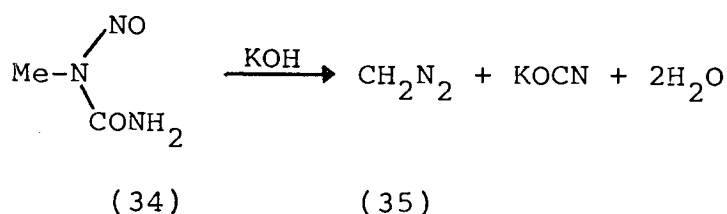
normal positive charge on carbon ($R_2-\overset{+}{C}-\bar{N}_2$).

Consequently, although diazomethane and diazoethane are unstable gases under normal atmospheric conditions, diazoalkanes having carbonyl, aryl, nitrile or fluorinated substituents are more stable and may be conveniently handled as liquids or solids.

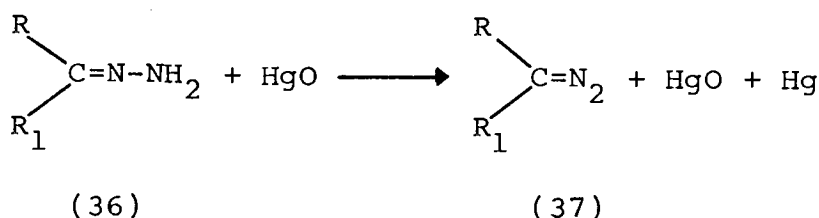
Synthesis

The original method of Curtius³⁹, the diazotisation of amines, requires a strongly electron withdrawing substituent on the α -carbon of the amine, and also an α -hydrogen.

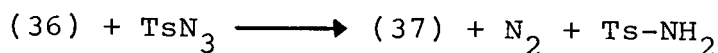
The classical method of preparation of diazoalkanes involves treatment of a nitroso compound of the general formula $R.CH_2.N(NO).X$ with a suitable base to yield the diazomethane $RCH-N_2$. For example diazomethane³⁵ is readily prepared by treating N-nitroso-N-methylurea (34) with base⁴³.



Disubstituted diazoalkanes (37) can be prepared by the oxidation of ketone hydrazones (36) with a variety of reagents including manganese dioxide⁴⁴, lead tetra-acetate⁴⁵, and mercuric oxide⁴⁶.



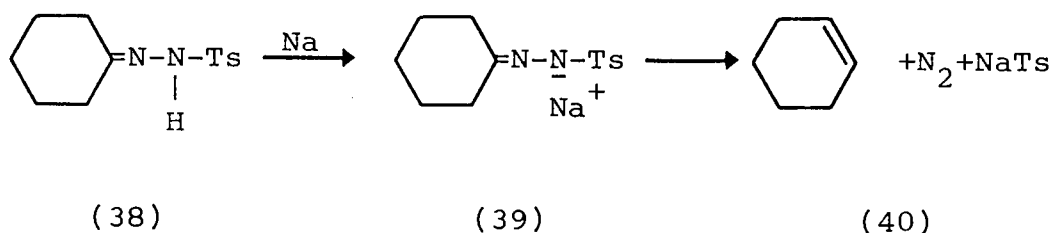
Hydrazones can also be converted into diazoalkanes by treatment with toluene-p-sulphonyl azide ⁴⁷.



The method used in this research programme involves the base induced thermal decomposition of tosylhydrazones as described below.

Base Induced Decomposition of Tosylhydrazones

It was observed by Bamford and Stevens ⁴⁸ that heating of non-enolisable tosylhydrazones (38) with base gave diazo-compounds or products of their decomposition e.g. alkenes. (40).

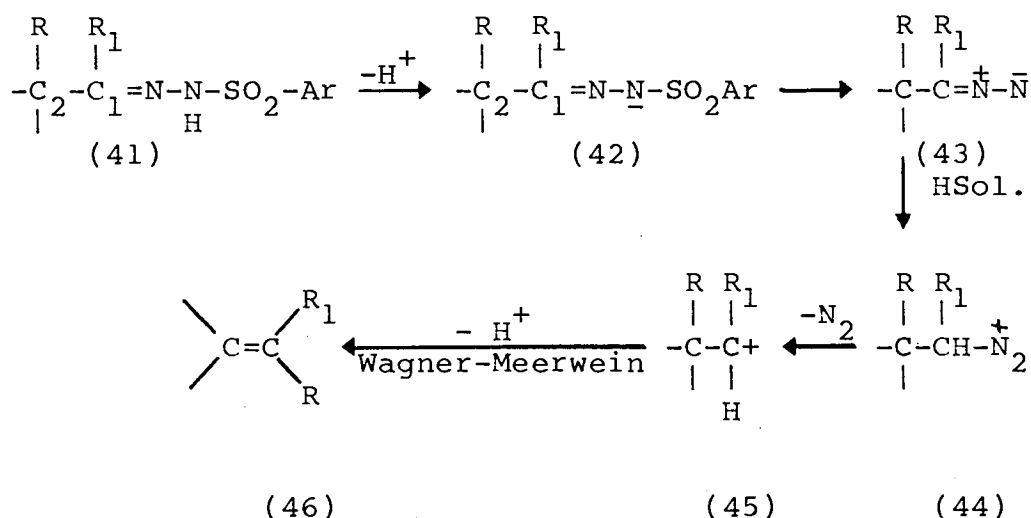


At lower temperatures substantial yields of the diazo-compounds could be obtained, from the tosylhydrazones.

The mechanism of the Bamford-Stevens reaction has been intensively studied and several reviews have appeared ⁴⁹⁻⁵³. A large number of parameters are important, including the ability of the solvent to donate and accept protons and the nature and concentration of base.

The rate determining step of tosylhydrazone decomposition was shown by Whiting ⁵⁴ to be a unimolecular elimination of the

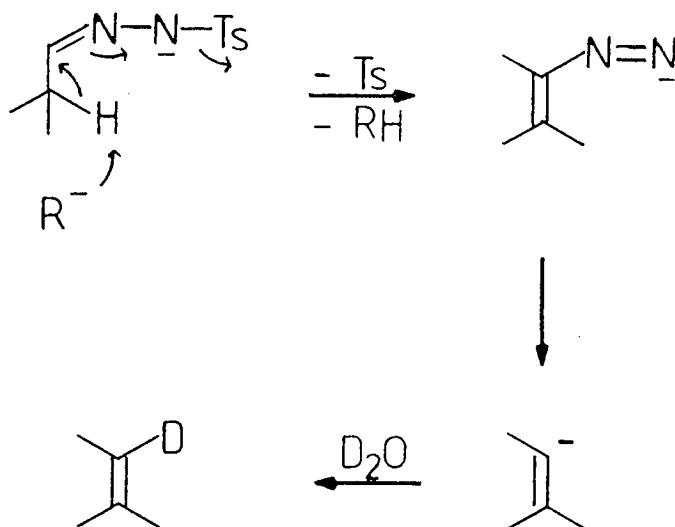
p-toluenesulphonyl anion from the anion of the tosylhydrazone (42) to give an aliphatic diazo-compound (43). It was also shown that in protic solvents protonation of the diazoalkane (at C-1) can occur followed by loss of nitrogen to give a carbonium ion which may then undergo a Wagner-Meerwein migration of a group from C-2 and loss of H^+ to give an alkene⁵⁴ (Scheme 8).



Scheme 8

Shapiro and co-workers⁵⁵ investigated the effect of base concentration and concluded that when a deficiency of base is used the unreacted tosylhydrazone acts as a proton donor so that an equilibrium between the diazonium cation and the diazo-compound is set up which lies on the side of the cationic species, and thus carbonium ion products predominate. When equimolar base is used the equilibrium lies on the diazoalkane side and so diazoalkane and products of their decomposition predominate.

Shapiro⁵⁶ and Friedmann⁵⁷ also showed that if excess strong base was reacted with tosylhydrazones at low temperature, then diazo-compounds were not involved but that an entirely different mechanism operated. Both workers showed that tosylhydrazones with α -hydrogen atoms gave good yields of alkenes. Deuterium was incorporated into the product when the reaction was quenched with deuterium oxide, in accord with the mechanism shown (Scheme 9).

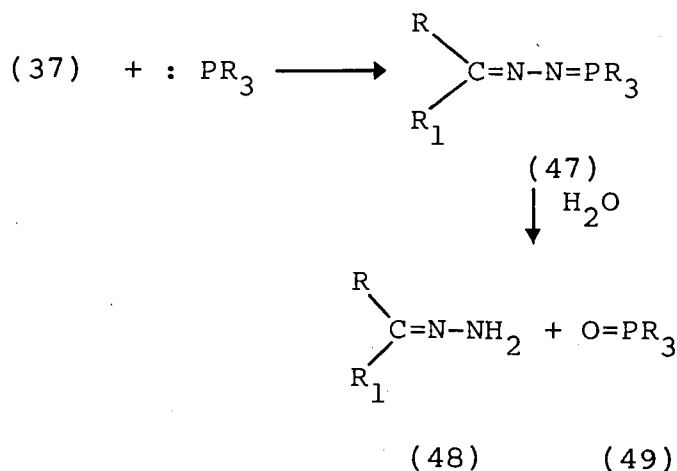


Scheme 9

The existence of the vinyl carbanion intermediate was confirmed by Shapiro⁵⁸ by chemically trapping the intermediate from fluorenone tosylhydrazone with deuterium oxide, ethyl bromide and carbon dioxide, to give 9,9-disubstituted fluorenes. This reaction has been much used as a source of vinyl carbanions.

Reactions

Diazoalkanes can sometimes be observed in reactions by their red colouration. They can be chemically trapped by their reaction with alkylphosphines⁵⁹ forming phosphazines (47) which on hydrolysis give hydrazone (48) and phosphine oxide (49) (Scheme 10).



Scheme 10

The last forty years have seen much interest in diazoalkane chemistry which has been reviewed^{60,61}. Much of this interest has derived from the ability of diazoalkanes to form carbenes via loss of nitrogen. However, another important aspect of diazoalkene chemistry is their ability to react without loss of nitrogen, under-going 1,3-dipolar cycloaddition.

2.2) Carbene formation

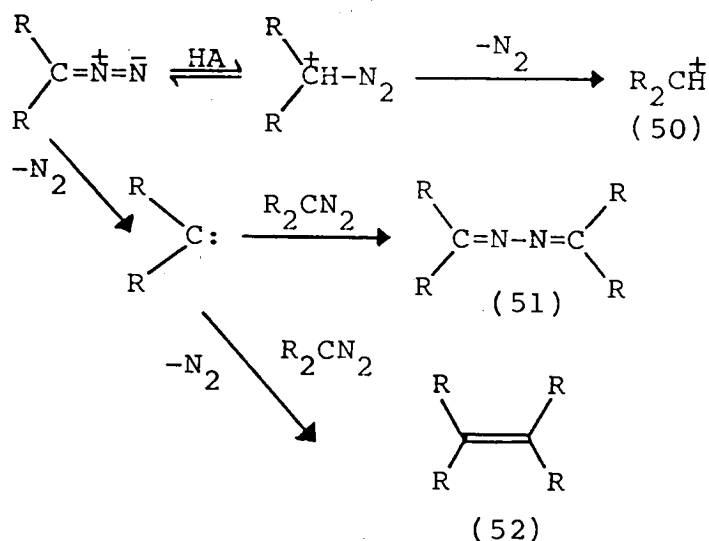
Carbenes are highly reactive, neutral species in which carbon is attached to two groups by covalent bonds and has two non-bonding electrons. These may have parallel spins and

occupy different orbitals (triplet state) or be spin paired (singlet state).

Carbenes have very short lifetimes (<1 second) and undergo a wide variety of reactions, including additions to alkenes, aromatic systems and other double and triple bond systems; insertions into carbon-hydrogen bonds; abstraction of hydrogen; rearrangements and dimerisation.

The reactions of carbenes have been well documented^{52,53} and carbenes are now recognised as the most common intermediates in the photochemical and thermal decompositions of diazoalkanes.

In the thermolysis of diazoalkanes, there are three common side-reactions of the diazoalkane which interfere with carbene generation (Scheme 11). Firstly, diazoalkanes are susceptible to protonation and carbenium ion production via loss of nitrogen. Also, carbene attack on the diazoalkane can occur, both with retention of nitrogen to give azine (51) or with loss of nitrogen to give a dimer (52).

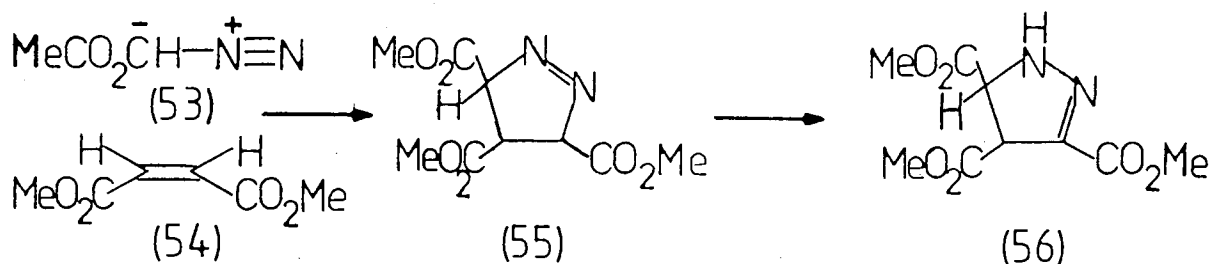


Scheme 11

In addition, the diazoalkane can add as a 1,3-dipole to any alkene or alkyne present to give pyrazolines or pyrazoles which may subsequently extrude nitrogen to give what are apparently carbene-derived products.

2.3) Intermolecular 1,3-dipolar cycloadditions

The formation of five-membered ring cycloadducts has been known since 1888⁶² when Buchner observed the addition of diazoalkanes (53) to α, β -unsaturated esters (54) to form 1-pyrazoline (35) which underwent rearrangement to the more stable 2-pyrazoline (56). Diazoalkanes readily react with sites of unsaturation to give five-membered rings which frequently undergo rearrangement, oxidation or extrusion reactions to give more stable, often aromatic, products.

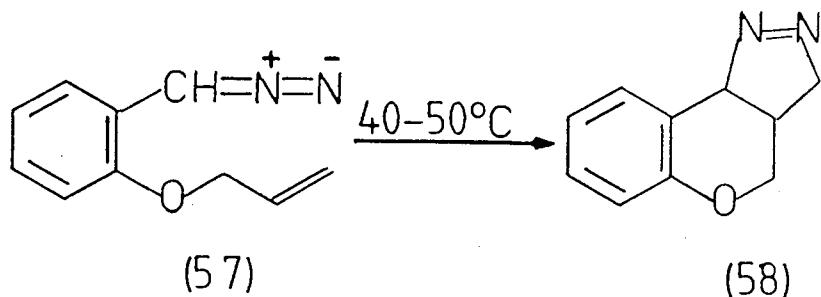


Scheme 12

Diazoalkanes are known to undergo intermolecular 1,3-cycloaddition with alkenes^{2,3,23} to form pyrazolines, alkynes^{24,73} to form pyrazoles and other unsaturated functions²⁵ which will not be discussed further as they are not of direct relevance to this thesis.

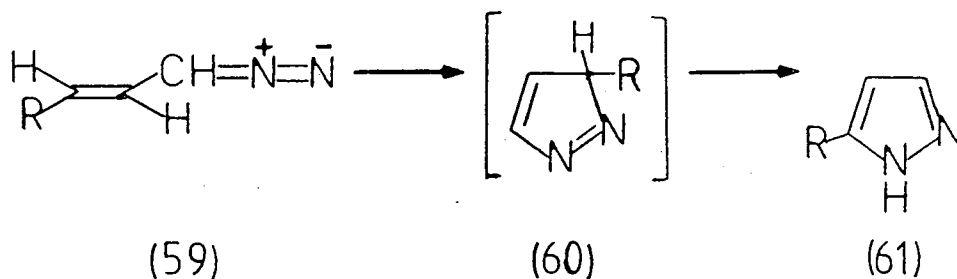
2.4) Intramolecular 1,3-dipolar cycloaddition

The first example of 1,3-dipolar cycloaddition was reported by Kirmse⁶³ who reported the synthesis of 1-pyrazoline (58) from diazoalkane (57) generated by the thermal decomposition of the corresponding tosylhydrazone sodium salt.



Other examples of intramolecular 1,3-dipolar cycloaddition of diazoalkanes have been reported^{64,74}.

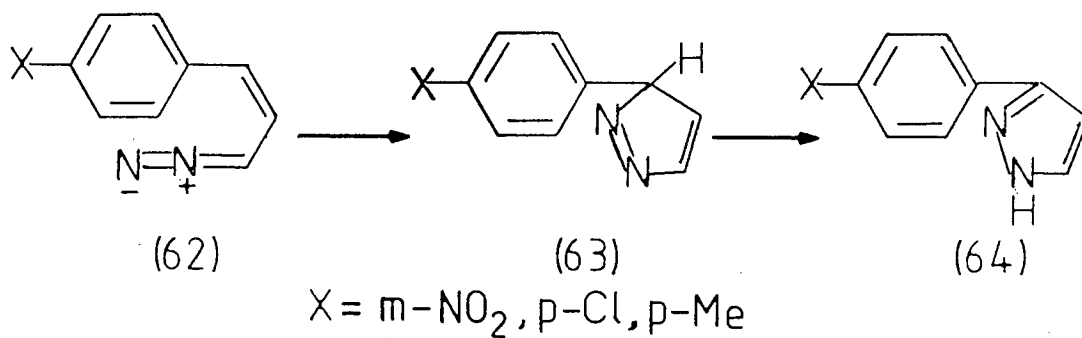
Conjugated diazoalkanes also undergo 1,5-dipolar electrocyclisation reactions. The first such reaction was reported by both Adamson and Kenner⁶⁵ and Hurd and Lui⁶⁶ who showed that 3-diazopropene (59, R=H) reacts slowly at room temperature to give the 3H-pyrazole (60) which undergoes a [1,5] hydrogen shift to give the isolated 1H-pyrazole (61).



Adamson and Kenner⁶⁵ also reported that the red colour of an ethereal solution of E-1-diazo-2-butene (59, R=Me) faded slowly at room temperature, the product being later identified⁶⁸ as 3(5)-methylpyrazole (61, R=Me).

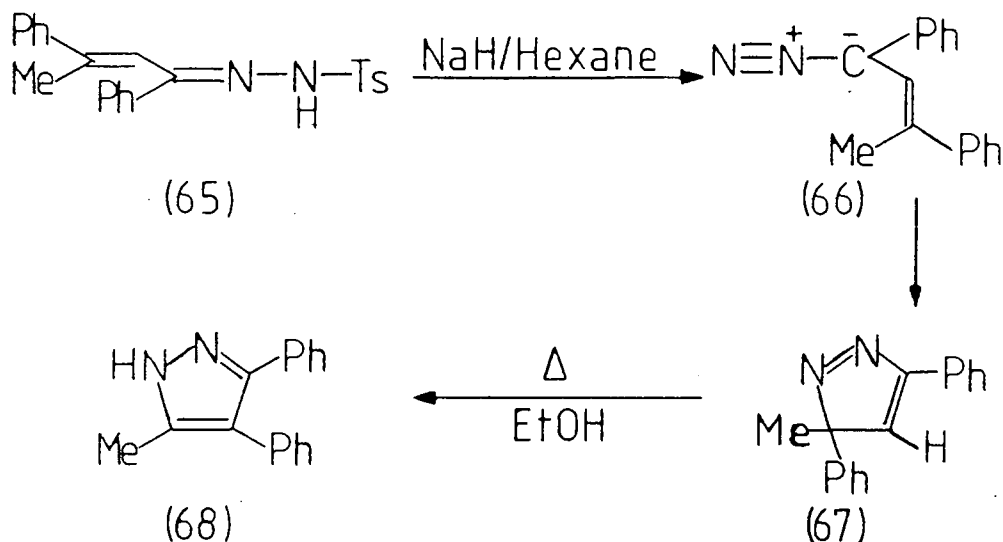
Ledwith and Parry⁶⁷ and Closs, Closs and Boll^{69,70} investigated the mechanism of similar cyclisations and concluded that intermediate (60) was involved.

Hart and Brewbaker⁷¹ concluded that cyclisation of diazoalkenes (62) to pyrazoles was indeed an intramolecular, concerted 1,3-dipolar cycloaddition, as the reaction rate was increased by aryl conjugation of the double bond and showed insensitivity to substituents in the aryl ring.



The nature of the products obtained is highly dependent upon the structure of the tosylhydrazone. The difference in behaviour in forming either pyrazole or hydrocarbon was postulated as being due to the degree of substitution at the β -carbon of the tosylhydrazone. The yield of hydrocarbon is good where the β -carbon is fully substituted with alkyl groups which sterically hinder cyclisation to the 3H-pyrazole and also accelerate elimination of nitrogen by electron release.

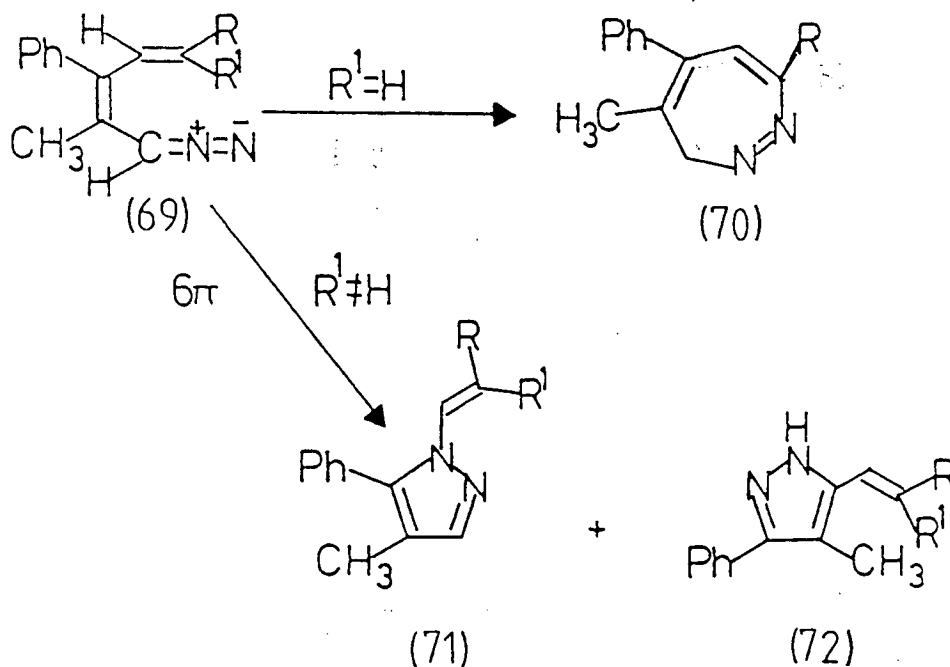
It was shown that thermolysis in hexane in the presence of sodium hydride of β -disubstituted tosylhydrazones (65) gave 3H-pyrazoles⁷² (67).



Scheme 12

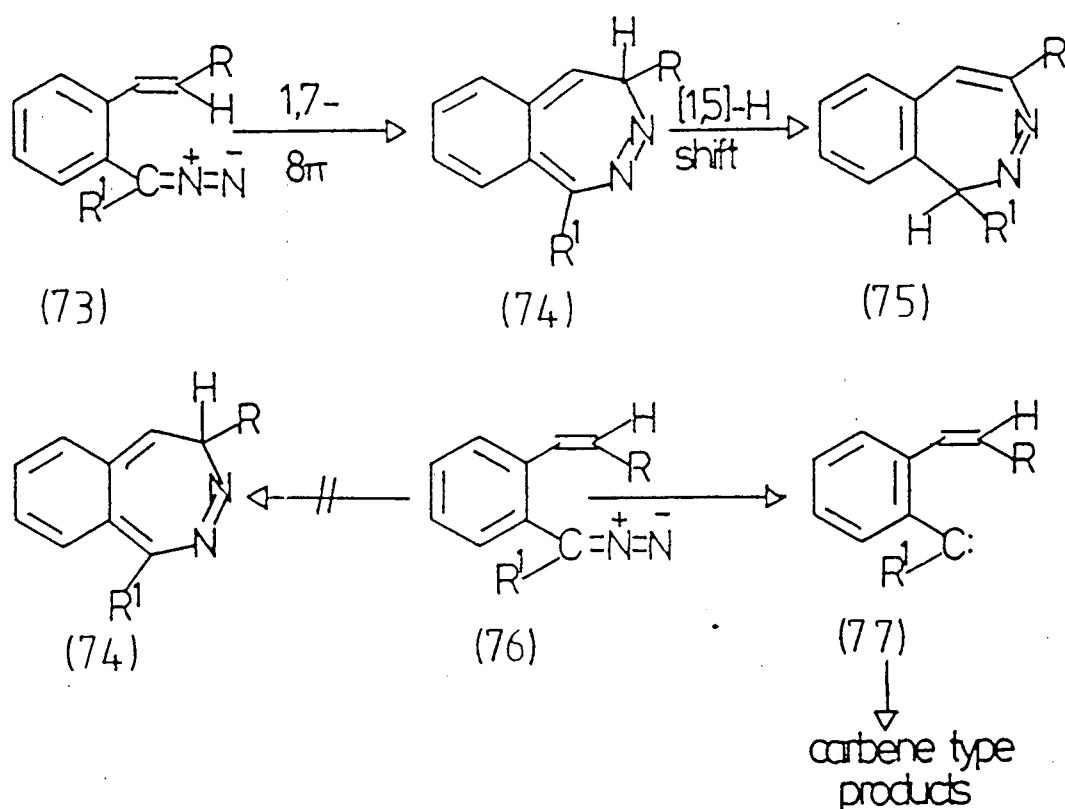
However these could be isomerised to 1H-pyrazoles (58) by heating in a protic solvent if one of the groups was migratable.

Diazoalkanes with $\alpha, \beta, \gamma, \delta$ -conjugation have been observed to undergo 1,5- and 1,7-electrocyclisations; the activation energies for these processes being not very different. The periselectivity in these systems is dramatically affected by the presence of an aromatic double bond in the conjugated system and also by the substituents on the terminus of the double bond. For example⁷⁵, the diazo compound (69), with olefinic double bonds in the α, β and γ, δ -positions, undergoes 1,7-electrocyclisation to give the 3H-1,2-diazepine (70) when $R^1 = H$, but undergoes a 1,5-electrocyclisation followed by successive [1,5]-vinyl and hydrogen migrations to give the pyrazoles (71) and (72) when $R^1 \neq H$ (Scheme 13).



Scheme 13

When there is an aromatic double bond in the α, β -position (73) once again 1,7-electrocyclisation, followed by a [1,5] hydrogen shift is observed when there is a cis-hydrogen, whereas, when there is no cis-hydrogen (76), the diazo-compound loses nitrogen and reacts via a carbene form (77), no 1,5- or 1,7-electrocyclisation being observed (Scheme 14)⁷⁶.

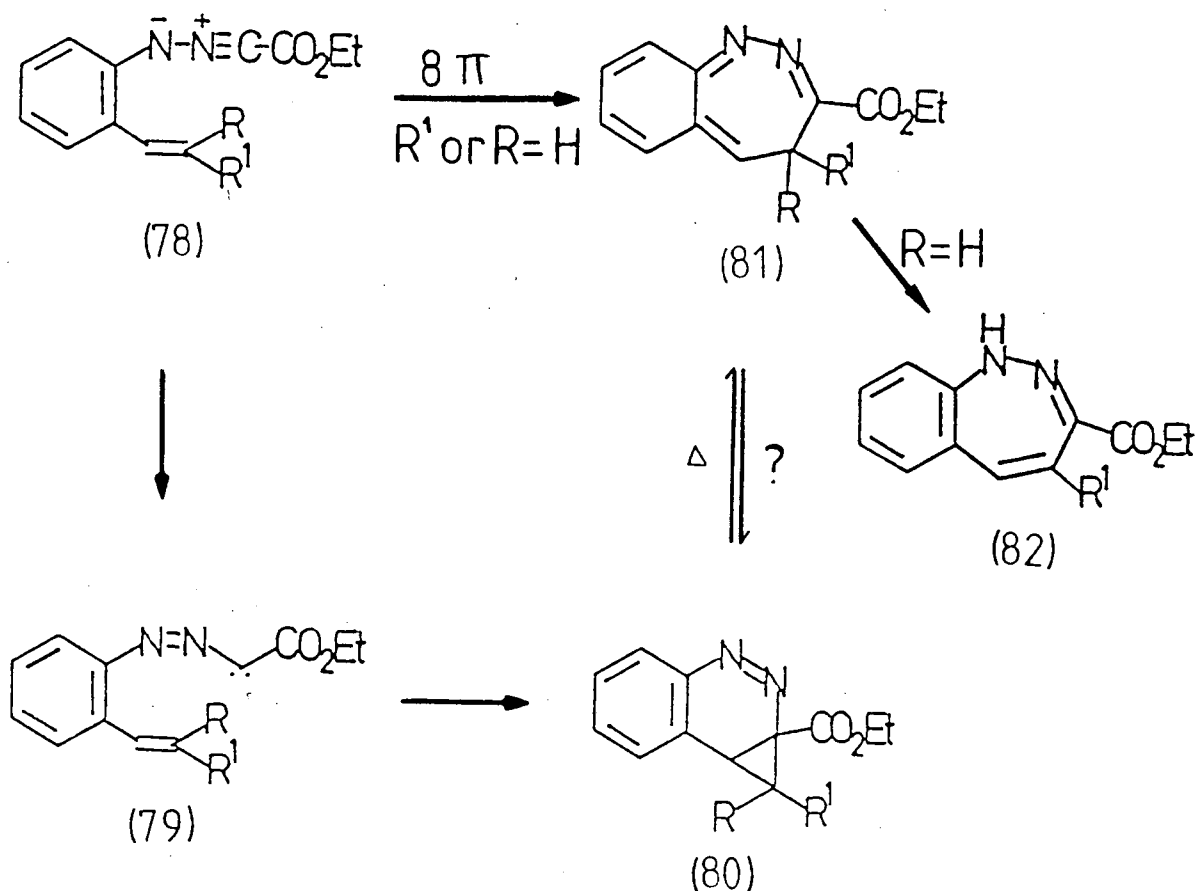


Scheme 14

This is in direct contrast to the reaction of nitrile imines (78), to give 1,2-benzodiazopines (82)^{82,83,84}, here the hydrogen on the alkene terminus may be either cis or trans (Scheme 15).

There are two possible pathways towards ring closure, firstly a 1,7-electrocyclisation followed by a [1,5] sigmatropic hydrogen shift. Secondly, a 1,1-cycloaddition of the nitrile imine (78) to the double bond to give a cycloprop [c] cinnoline (80). Further heating converts (80) to the benzodiazopine (82), provided that R^1 or $\text{R}=\text{H}$.

The intermediate (80) has been isolated by carrying out the reaction at room temperature in the presence of silver carbonate. Its formation is entirely stereospecific the E- and Z- starting nitrile imines giving the exo and endo products respectively.



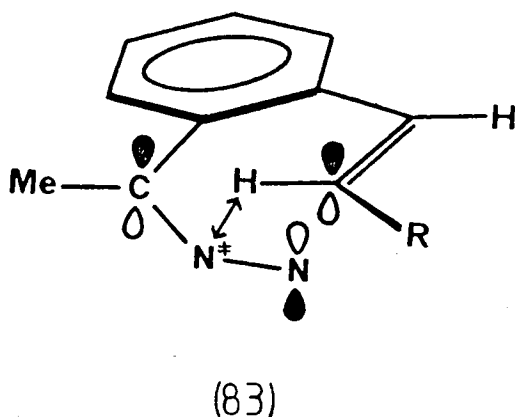
Scheme 15

Since only the hydrogen on the alkene terminus may only be trans in the reaction of diazo-compounds we may assume that these reactions are indeed 1,7-electrocyclisations and do not proceed via 1,1-cycloaddition followed by electrocyclic ring opening.

It can also be seen that steric hindrance alone is preventing 1,7-electrocyclisation of (76) since no formation

of the common intermediate (74) can occur, otherwise 1H-2,3-benzodiazopine (75) would be obtained.

To account for these experimental observations Sharp^{75,77} has postulated that 1,7-electrocyclisation proceeds via a helical transition state (83) which has an easily accessible geometry which brings the terminal atoms into a bonding overlap and requires only the minimum angular distortion of the diazo group from its preferred linear geometry. This transition state has the nodal properties of Ψ_4 of a heptatrienyl anion and so formally requires a controtary ring closure.

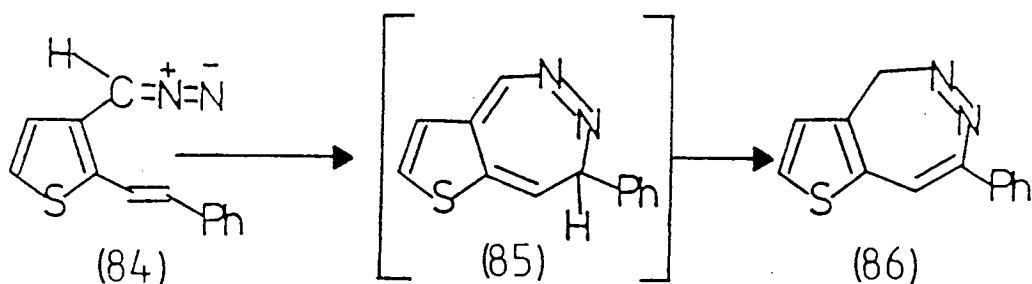


In this transition state the steric interaction [\longleftrightarrow in (83)] between the cis hydrogen atom and N^+ of the diazo group is small and will not impede the approach of the terminal atoms. However, a methyl group at this position comes into a significant steric interaction with N^+ . This will raise the activation energy for 1,7-electrocyclisation either by inhibiting orbital overlap between the terminal atoms or by twisting the γ, δ -double bond out of conjugation.

The propensity for 1,7- as opposed to 1,5-electrocyclisation in the diazo-compound (69) can readily be explained in terms of the high degree of bending of the diazo group required in the transition state for 1,5-electrocyclisation.

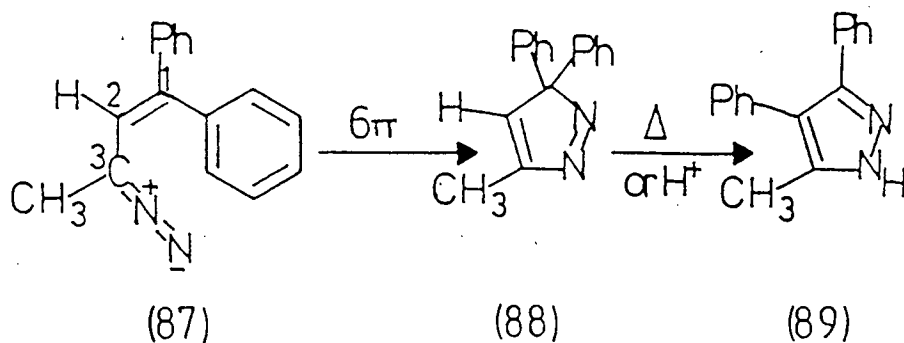
Calculations have shown that there is a considerable energy barrier to in-plane bending for diazoalkanes ¹¹.

The α,β -double bond in diazo-compounds of the type (73) may also be part of a heterocyclic ring ⁷⁸, for example, the 2,3 bond of thiophene (Scheme 16), but not the 3,4 bond which does not have sufficient double bond character to allow an electrocyclicisation process to occur.



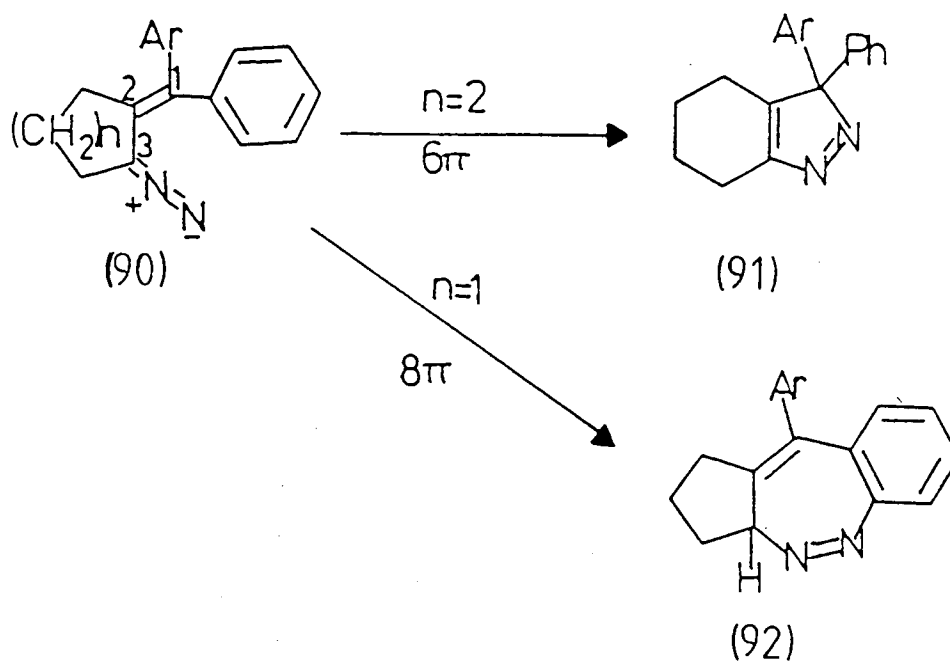
Scheme 16

When the α,β bond is olefinic and the γ,δ is aromatic then 1,5- or 1,7-electrocyclisation can be observed ^{79,80}, depending upon the substituents present on the α,β bond. In the simple acyclic case the diazo-compound (87) reacted to give pyrazoles (89) exclusively (Scheme 17).



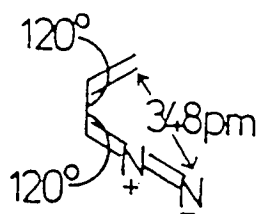
Scheme 17

Fusion of a cyclohexyl ring at C2-C3 (90, $n=2$) also led to the formation of pyrazoles (91) whereas the fusion of a cyclopentyl ring at C2-C3 (90, $n=1$) led to a complete change in periselectivity, the benzodiazopines (92) being the only observed product (Scheme 18)⁷⁹.

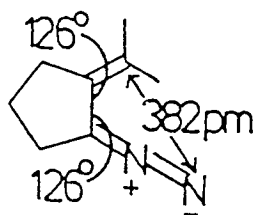


Scheme 18

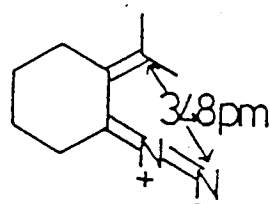
This difference in periselectivity was rationalised in terms of greater separation of the termini in the cyclopentyl fused compound (93) requiring a greater distortion of the diazo group to achieve cyclisation. This distortion has a large energy barrier and so, the 1,7- becomes preferable to 1,5-electrocyclisation. The ring closure also leads to a more strained product, a 5,5-fused system, than that formed from the cyclohexyl fused compound (94) which also has a smaller separation between the termini of the π -system.



(87)

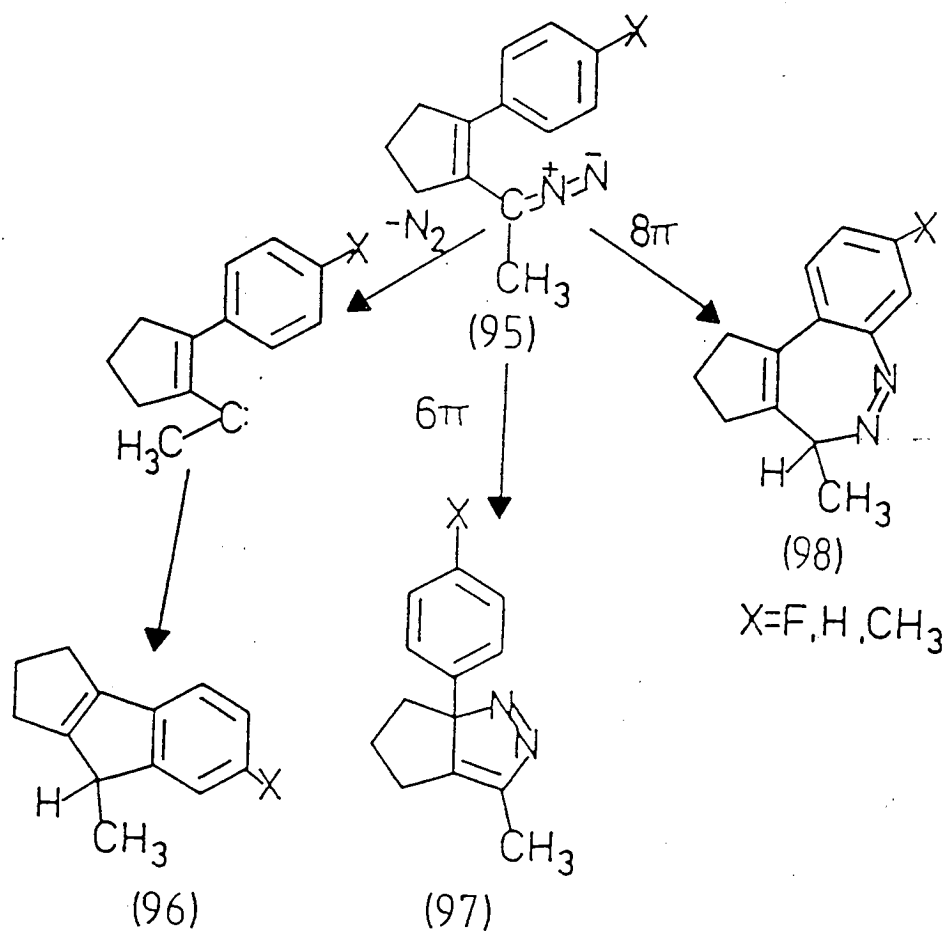


(93)



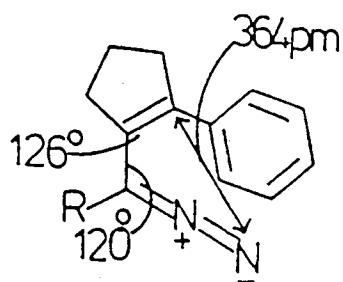
(94)

Fusion of a cyclohexyl ring at C1-C2 also produced only the pyrazole but when a cyclopentyl ring was fused at C1-C2 the diazo-compound (95) reacted via all three modes of reaction to give (96), (97) and (98) (Scheme 19)⁸⁰.



Scheme 19

This was the first example of a 3-aryl-1-diazoalkene reacting by both 1,5- and 1,7-electrocyclisation. This effect can be attributed to the fact that in (99) the termini separation is slightly greater than in the acyclic case (87) but not as great as in (93). So, in contrast to (93), both 6 π - and 8 π -electrocyclisations are possible and the carbene reactions are also competitive since the diazo-group is not necessarily in conjugation with the α, β bond due to free rotation about the single bond.



(99)

Finally, when both the α, β and γ, δ bonds are aromatic no 1,5- or 1,7-electrocyclisation is observed and the only products are those derived from carbene⁸¹.

3) ASYMMETRIC INDUCTION

3.1) History

The term "asymmetric induction"* was introduced by Erlenmeyer⁸⁵ in 1912 to explain his alleged successes in "inducing" optical activity in various unsaturated compounds such as benzaldehyde and cinnamic acid by heating them with tartaric acid in the presence or in absence of a solvent.

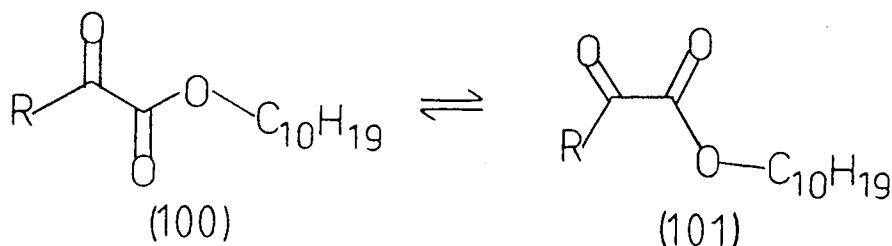
Although Erlenmeyer had attempted the induction of optical activity in molecules which to us, are clearly not dissymmetric, other workers were concerned with using asymmetric induction in the attempted conversion of a symmetrical molecule into a dissymmetric molecule in a solution of optically active solvent. As long ago as 1896, Boyd⁸⁶ reduced benzoylformic acid in an aqueous solution of tartaric acid. Kipping⁸⁷ in 1900 performed the benzoin synthesis in the presence of d-camphor. In these and many subsequent investigations^{88,89}, no activity was induced by the non-reacting asymmetrical material.

In 1932, Kortum⁸⁸ gave his interpretation of the meaning of the term asymmetric induction as follows: the action of a force exerted by asymmetric molecules on molecules capable of changing from a symmetrical into an asymmetrical configuration.

* Defined by Eliel⁹⁰ as the production of a new asymmetric atom or entire dissymmetric molecule under conditions where two stereoisomers are formed in unequal amounts.

In 1936, McKenzie⁹¹ commenting on critics' dismissal of the Erlenmeyer conception of asymmetric induction, said:

"Nevertheless whether the idea of asymmetric induction is right or wrong, it has since proved itself of service in the study of asymmetric synthesis, and today it ought not to be at once dismissed as both useless and superfluous." He then applied the term to a long series of reactions between L-methyl benzoylformate or L-menthylpyruvate and Grignard reagents. McKenzie considered that in the optically active esters the carbonyl group in the alpha-position might assume a dissymmetric conformation under the influence of an optically active radical.



McKenzie suggested that the two forms (100) and (101) were present in unequal amounts, thus explaining the success of the asymmetric synthesis in generating an enantiomeric excess of the resulting alpha-hydroxy acids. He also went further and used it to explain why all benzoylformate reactions gave laevorotatory acids and all pyruvate reactions gave dextrorotatory acids.

However the idea of asymmetric induction, in the sense of a double bond made dissymmetric prior to approach of the reagent, as the cause of an asymmetric reaction was not accepted and the partial stereospecificity of the reaction was

attributed to first order asymmetric transformation of optically unstable intermediates.

Other theories such as that suggested by Price⁹² attempted to explain that the electronic activation of the double bond was responsible for asymmetric induction in chemical reactions.

Turner and Harris⁹³ in 1947 gave some general outlines for asymmetric induction as follows: in order that a fixed centre of asymmetry shall influence the steric course of an addition reaction at an unsaturated centre in the same molecule in an asymmetric synthesis, there must be some stage at which either stereoselective addition occurs as an irreversible process. Thus, in the addition of XY to a carbonyl group of a molecule already containing a fixed centre of asymmetry (in group R), the first stage may be regarded as the approach of (X^-) towards the positive end of the polarized group (Figure 6).

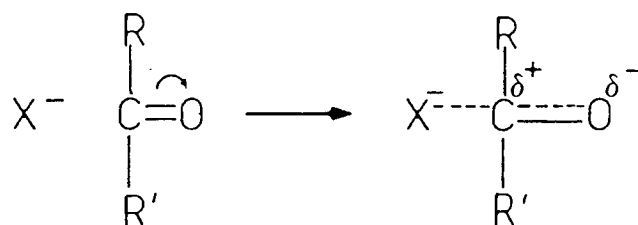
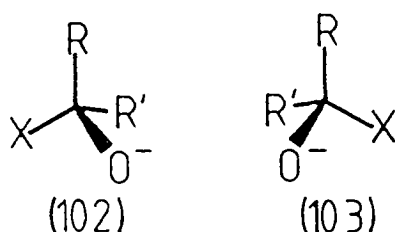


Figure 6

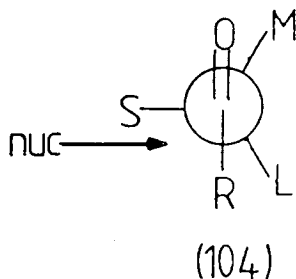
The two tetrahedral arrangements (102) and (103) are possible before the addition of Y^+ .



If the energy changes concerned in the formation of these two structures are equal, there is no immediate asymmetric addition. If they are unequal, then we have asymmetric addition which appears to take place even in non-reversible asymmetric reactions (e.g. Grignard reactions).

It was not until the work of Cram⁹⁴ and also that of Curtin⁹⁵ in 1952 that a rationalisation of asymmetric synthesis by asymmetric induction was first attempted using experimental evidence. Their studies of the stereochemical course of the addition of organometallic and metal hydride reagents to ketones having chiral centres next to the carbonyl function resulted in the generalisation now known as Cram's rule.

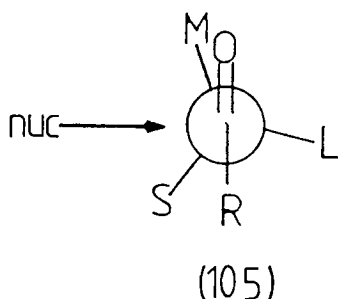
In (104), wherein (L), (M), and (S) represent the large, medium sized and small group (hydrocarbon radical or hydrogen atom) respectively, attached to the chiral alpha-carbon.



Formally the molecule is so orientated that the carbonyl group is flanked by the two smaller alpha-substituents (M and S), the largest (L) being eclipsed with the alkyl group (R) on the other side of the carbonyl function. The Grignard reagent or alkyl lithium then approaches from the side of the smallest substituent (S). This model was used also by Boeckman⁹⁶ to predict the selectivity in the epoxidation of allylic alcohols. (M=OH).

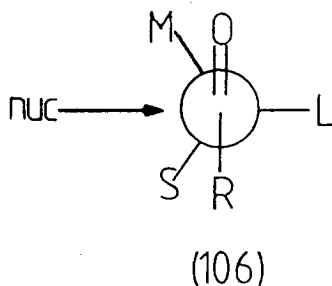
However this model probably does not correspond to the mechanistic one; several alternative mechanistic rationalisations have been provided since 1967.

Karabatsos⁹⁷ suggested a model based on the assumption that a conformation similar to that of the isolated carbonyl is maintained in the transition structure (105).



Chautemps-Pierre⁹⁸ and Kishi⁹⁹ have used this model also to predict the selectivity found in the epoxidation of allylic alcohols using peracids. The model was also used by Kishi¹⁰⁰ in the hydroboration of alkenes.

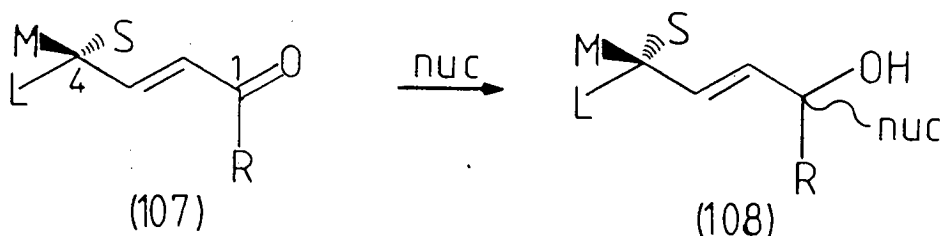
A year later the Felkin model¹⁰¹ (106) was advanced, later refined by Anh¹⁰² and Houk¹⁰³, best agrees with predictions based on ab initio calculations.



In this model, (L) represents either the largest group or the group whose bond to the alpha-carbon (L-C) provides the greatest σ^* overlap with the carbonyl π^* orbital. The stereoselectivity of this type of reaction has been surveyed by Morrison and Mosher¹⁰⁴ and is generally not very high.

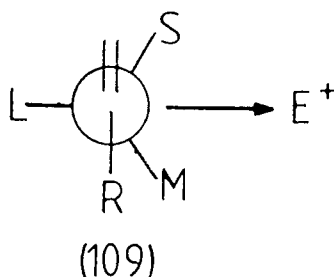
Other models have been postulated, but many are chelation or cyclic models and have no relevance to this thesis. Applications of such models have been well documented¹⁰⁵.

Fleming¹⁰⁶ has attempted to find a 'vinylogous Cram's rule' to determine whether diastereoselectivity is governed by steric or electronic factors.



In structure (107) the chiral centre is held spatially away from the centre undergoing reaction, but is conjugated to it. In this situation electronic information might be relayed to the prochiral centre (C-1) but steric information cannot. However, Fleming's search was in vain and he concluded that Cram's rule diastereoselectivity is probably steric in origin.

Most of the work over the last 30 years has dealt with the diastereoselectivity of nucleophilic attack. The diastereoselectivity of electrophilic attack, in open chain structures, on trigonal carbon adjacent to a chiral centre has received much less attention, until Houk and his co-workers¹⁰³ proposed a rule as shown in (109).



The preferred conformation in the transition structure has the small group (S) eclipsing (or partially eclipsing the double bond, and the electrophile attacking the double bond on the less hindered side, antiperiplanar to the large group (L).

It follows that electrophilic attack should take place from the opposite side to that of the corresponding nucleophilic attack on a carbonyl group, and that the electrophile rule other things being equal, should prove to be the opposite of Cram's rule.

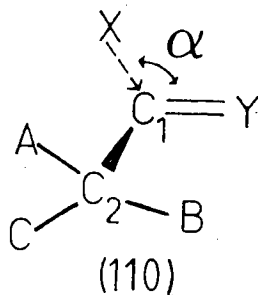
Most of the known examples of open chain diastereoselective electrophilic attack are not strictly covered by this rule, because the chiral centre carries on oxygen function which either delivers the reagent (e.g. epoxidation⁹⁸ or Simmons-Smith reaction¹⁰⁷ on allylic alcohols) or exerts a substantial, but not entirely consistent, electronic effect (allylic ethers react with osmium tetroxide¹⁰⁸, or nitrile oxides¹⁰⁹ consistently in one sense, but with hydroborating agents¹¹⁰ in the other). The alkylation of enolates¹¹¹ with a beta-oxyanion probably involves a chelate and is not a true open-chain reaction. Halogen attack, although much studied (in halolactonisation¹¹² for example) presents difficulties in identifying which step, electrophilic attack or opening of the intermediate determines the

stereoselectivity. Hydroborations of some alkenes^{113,114} electrophilic attack on allyl silanes¹¹⁵, alkylation of beta-silyl and beta-stannyl enolates^{116,117} and alkylation and protonation of enolates¹¹⁸ are the best examples of reactions showing high diastereoselectivity in conformity with this rule.

3.2) Ab Initio Studies of Transition Structure Conformations

These theoretical investigations by Houk^{103,119} into the transition structure conformations have been developed from theoretical generalisations about the following:

- (i) the angles of attack, α , of reagents, X, upon multiple bonds (110).
- (ii) the rotational preferences about the C_2-C_1 bonds of transition structures.
- and (iii) the preferred locations of allylic substituents A, B, and C in the transition structures.



If C_2 is a chiral centre, and if one conformation of the allylic bonds is highly preferred, then there are six different ways to place A, B, and C on the allylic positions (Figure 7).

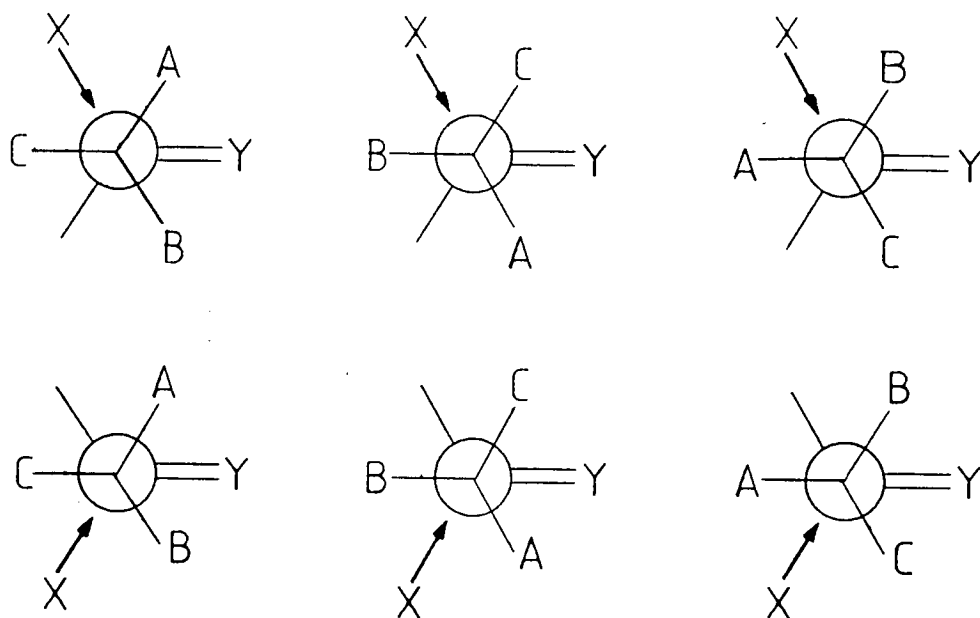
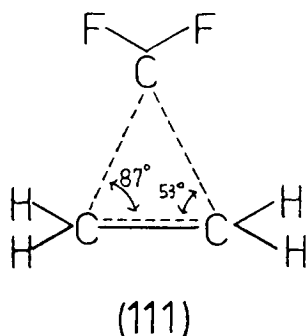


Figure 7

Three of these correspond to attack on one face of the C=Y bond, and the other three correspond to attack on the opposite face. To predict the stereoselectivity of such a reaction, the relative energies of these six conformations must be predicted with a high degree of accuracy.

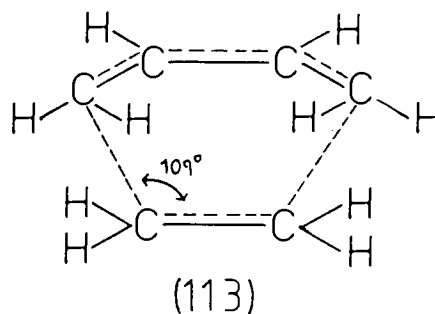
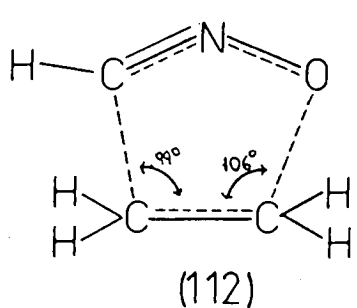
Transition structures for reactions that are representative of electrophilic addition to substituted alkenes were obtained by gradient searches with ab initio calculations and the 3-21G basis set using the current version of GAUSSIAN 80 and 82, a series of computer programs developed by Pople¹²⁰.

Studies^{113,121} have revealed that for electrophilic attack on the multiple bond, an acute angle of approach is favoured (in nucleophilic attack, the preferred attack angle is obtuse). For example, the carbene cycloaddition of CF₂ with ethene¹²¹, (111).

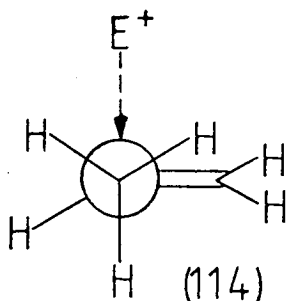


In the transition structure for electrophilic addition, the alkene C-C is stretched, but the geometry is otherwise relatively unperturbed.

Pericyclic reactions such as the 1,3-dipolar cycloaddition of fulminic acid to ethene (112) and the Diels-Alder reaction of butadiene with ethene (113), nearly tetrahedral α 's are predicted¹²².



Calculations have also been performed to assess the conformation preferences with respect to single bonds attached to atoms undergoing bonding changes in transition structures^{103,123}. For example, the methyl group in (114) are staggered with respect to the bond forming and to the remaining two remaining bonds being attacked.



These results show that conformations of substituents in transition structures may be quite different from these in reactants e.g. an alkene has one allylic bond eclipsed with the double bond in the ground state, but the transition structure conformations are more product like.

Rotational barriers involving torsional interactions with partially formed bonds are nearly as large as these involving fully formed bonds. Consequently, the assumption of staggering in transition state is just as reasonable as the assumption of staggering in stable molecules. Thus as in Figure 7 in the attack of reagent (X), the allylic chiral centre has 6 possible staggered conformations (non-staggered conformations can be safely assumed to be higher in energy).

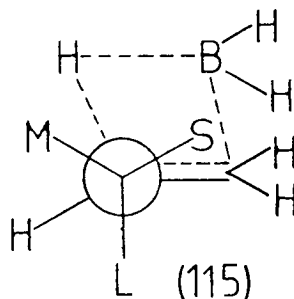
Experimental results show which diastereomer is favoured but gives no direct information about which of the staggered transition structures is lowest in energy. However, the theoretical studies complemented by experimental studies has led to generalisations about which of the six transition structures shown in Figure 7 are favoured. (See page 67 of this thesis).

When an allylic centre bears three groups of different size but not of greatly different electronic character, the preferred product arises from the transition state that has the largest group in the least crowded position. Two factors are mainly responsible for these conformational preferences, steric effects and electronic effects.

Steric effects:

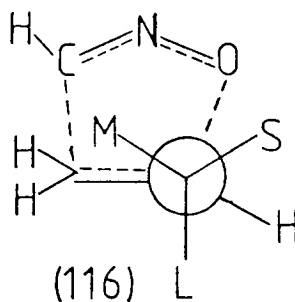
In hydroborations, there is a great preference for the

conformation that has the (L) group anti to the attacking electrophile, the (M) group 'outside' (away from the double bond) and the (S) group 'inside' (near the double bond) in (115).



This 'inside crowded' model is sometimes referred to as "anti-Cram" because it is opposite to the stereochemistry predicted by Cram's rule (i.e. in nucleophilic additions the (M) group occupies the 'inside' position). This "inside crowded" preference will hold, in general, whenever the 'inside' position is more crowded than the outside.

In nitrile oxide cycloadditions such as (116), the 'outside' position is more crowded than the 'inside'.

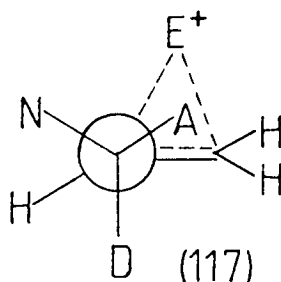


The 'outside crowded' model correctly predicts the preferred products of nitrile oxide cycloaddition¹²⁴ and hexachlorocyclopentadiene Diels-Alder reaction¹²⁵ and will probably prove to

be general for reactions with 5 - and 6-membered transition states.

Electronic effects

When allylic substituents are either electronegative or electropositive relative to hydrogen, electronic effects cause these substituents to orientate in a specific fashion with respect to the attacking reagent. On the basis of model calculations^{113,126} the following generalisations for electrophilic attack can be made.



In (117) the most electropositive group (D) should be anti to maximise electron donation from the high-lying σ_{C-D} orbital to the transition state LUMO, which consists of electrophile LUMO mixed with the alkene HOMO. The 'outside' position is second best, and the donor avoids the 'inside' position, where σ_{C-D} overlap with π^* will be negligible. The electronegative group (A) prefers the 'inside' or 'outside' positions. The interaction of σ_{C-A}^* with the alkene HOMO will stabilise the latter and decrease its interaction with the electrophile LUMO. In other words, C-A favours the 'inside' or 'outside' positions to minimise electron withdrawal by σ_{C-A}^* from the already electron deficient transition state. Whether 'inside' or 'outside' is the best location for (A) depends on the specific dihedral angles as

well as the interactions between the attacking electrophile and groups at the 'inside' or 'outside' positions.

For example, in the reaction of nitrile oxides with chiral allyl ethers, the alkoxy group always occupies the 'inside' position¹²⁶ irrespective of the size of the alkoxy group. Other factors such as chelation or hydrogen bonding of the electropositive group with the incoming electrophile may result in the adoption of the opposite conformation from that predicted. Similarly, intramolecular reactions may permit the connecting chain to adopt only the 'inside' or 'outside' conformations. The following section gives examples of all these effects in greater detail.

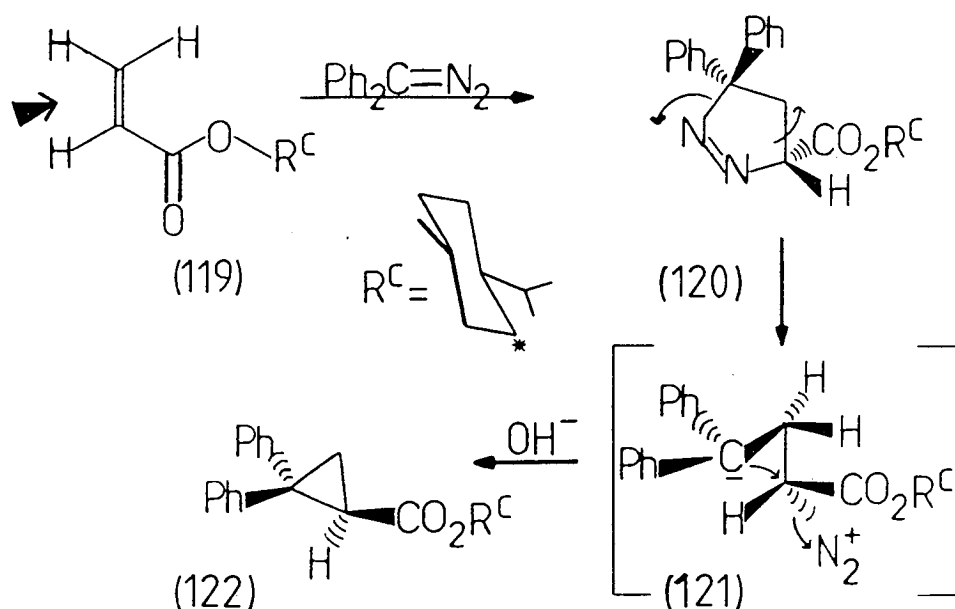
3.3) Asymmetric Induction in [3+2] Cycloaddition reactions

The intention of this section is to illustrate the breadth of [3+2] cycloaddition processes to which the asymmetric principle has been applied and the highest levels of efficiency attained. However, the number of reports is simply too numerous to mention and only those of direct relevance to this thesis will be discussed.

3.3.1) Diazoalkanes

A classical work of asymmetric induction in the 1,3-dipolar cycloaddition of diphenyldiazomethane with menthyl acrylate (119) was reported by Walborsky and his co-workers¹²⁷ in 1959 (Scheme 21). When the 1,3-dipole is allowed to react with (119) and the products are directly saponified, the optically active cyclopropanecarboxylic acids (122) were obtained at 2%e.e..

Walborsky¹²⁸ rationalised the stereochemical outcome in terms of an ^{anti}Prelog-type model, with [3+2]-cycloaddition occurring preferentially from the less hindered diastereotopic face of the double bond to furnish the pyrazoline (120).

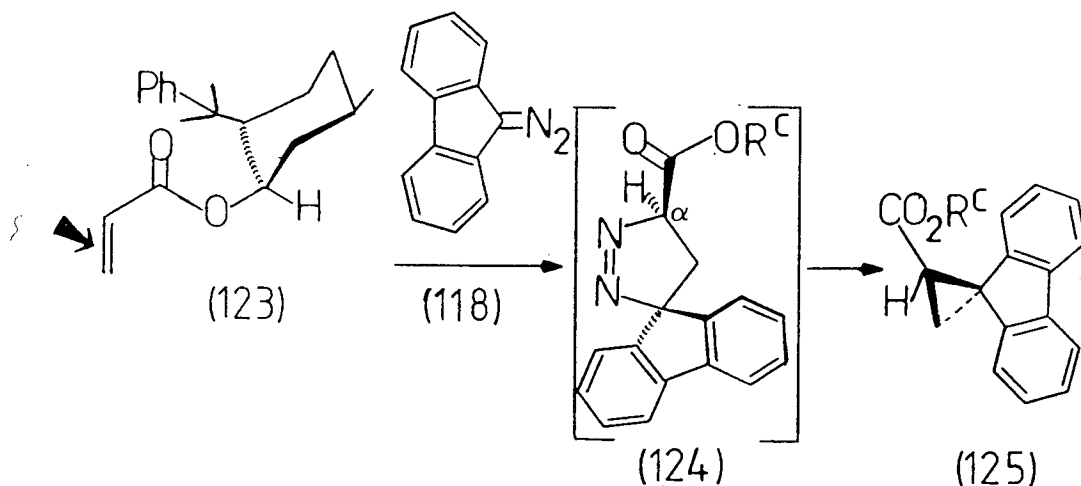


Scheme 21

Subsequent opening of (120) to zwitterion (121) and reclosure with ejection of nitrogen satisfactorily accounts for the predominance of the R enantiomers.

However this mechanism has been recently disputed by Oda and his co-workers¹²⁹. According to their mechanism, it would be expected that a higher selectivity for the anti-Prelog products would be obtained by substituting the sterically bulkier 8-phenylmenthyl group for the menthyl group. In fact, a preferential Prelog-type attack was observed with a 21% ee.

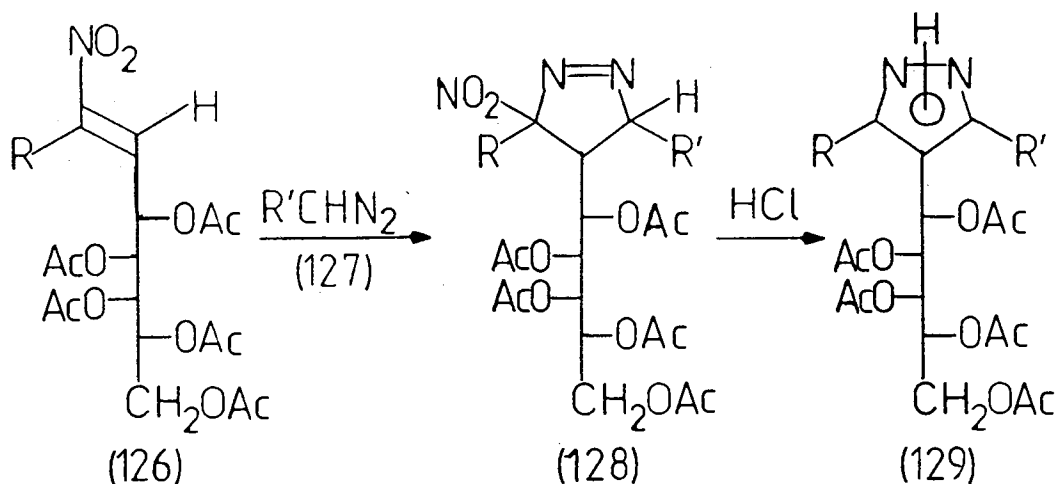
The observed selectivity for (123) was rationalised by Oda (Scheme 22). Preferential Prelog-type attack of (118) to (123) gives the pyrazoline (124).



Scheme 22

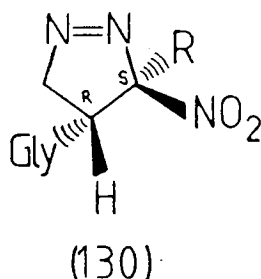
Subsequent extrusion of nitrogen and ring closure with retention of the configuration at C_α affords the (2S)-cyclopropane (125).

Galbis and his co-workers¹³⁰ have examined the cycloaddition of diazoalkanes with sugar nitro olefins (126) yielding pyrazolines (128) which were aromatised to pyrazoles (129) which are useful acyclic sugar C-nucleosides. (Scheme 23).



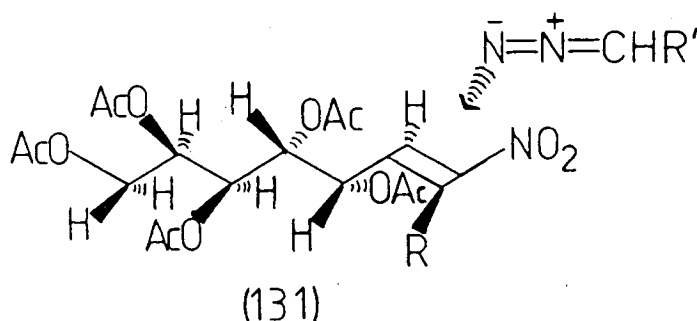
Scheme 23

When diazomethane (127) $R'=H$ is used as the 1,3-dipole and reacted with (126), $R=H$, a single isomer is obtained in 86% yield (130) $R=H$.



The reaction of diazomethane with (126) $R=Me$ yielded quantitatively two possible regioisomers in the ratio 9:1. The major isomer being similar to that shown in (130), $R=Me$.

In both cases the diastereomers originated by addition of diazomethane to the less hindered face of the nitro olefin (131).



This is believed to be the favoured conformation of the sugar molecule in solution, thus one face of the nitro olefin is sterically hindered by the bulky sugar chain.

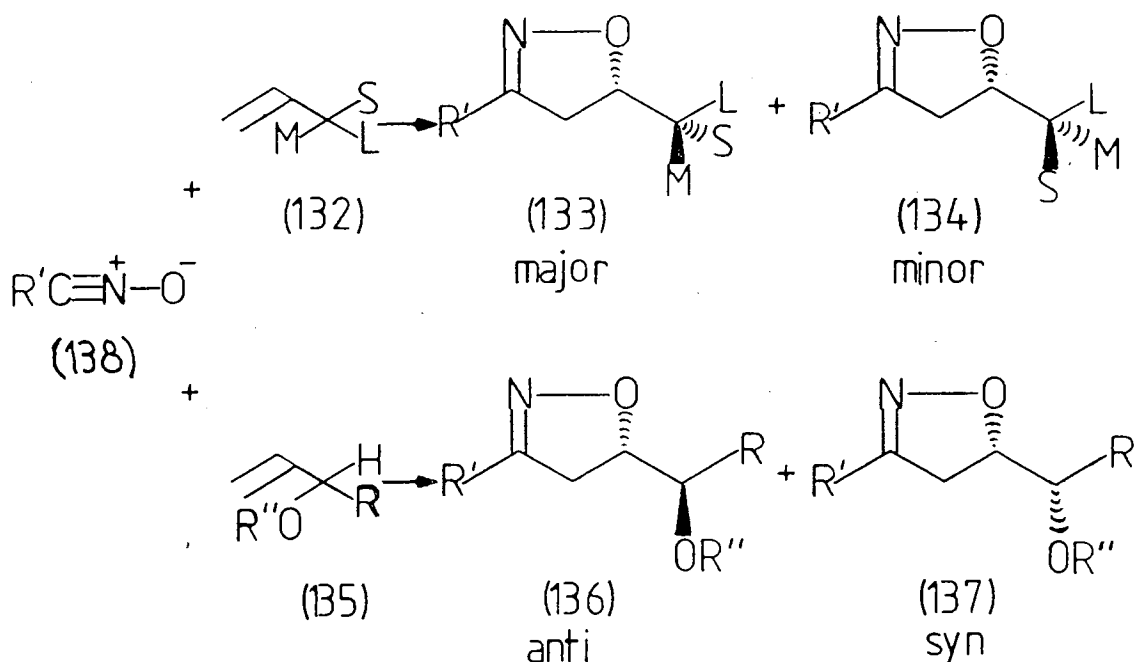
Similarly the reaction of diazoethane (127) $R=Me$ with (126) $R=Me$ and (126) $R=H$ gave single diastereomers like (130) in high yields again by addition of the diazoethane to the less hindered face of the nitro olefin.

The reaction of diazoacetate (127) $R' = \text{CO}_2\text{Et}$ with (126) $R = \text{Me}$ (126) $R = \text{H}$ give only low yields of the pyrazole (129) $R = \text{Me}$ and (129) $R = \text{H}$ respectively. None of the pyrolazolines (128) was isolated.

3.3.2) Nitrile oxides

Intermolecular Nitrile oxides cycloaddition

1,3-Dipolar cycloaddition of nitrile oxides to alkenes provides a valuable tool for the synthesis of 2-isoxazolines as natural products and as unnatural compounds possessing a biological activity^{133,135}. Attempts to simultaneously control relative and absolute stereochemistry by use of chiral nitrile oxides¹³⁶⁻¹³⁷ have met with limited success so far. However, a great deal of attention has been devoted to the study of stereoselectivity of the nitrile oxide cycloaddition to alkenes bearing a stereocenter in the allylic position. The trends are summarized in Scheme 24.

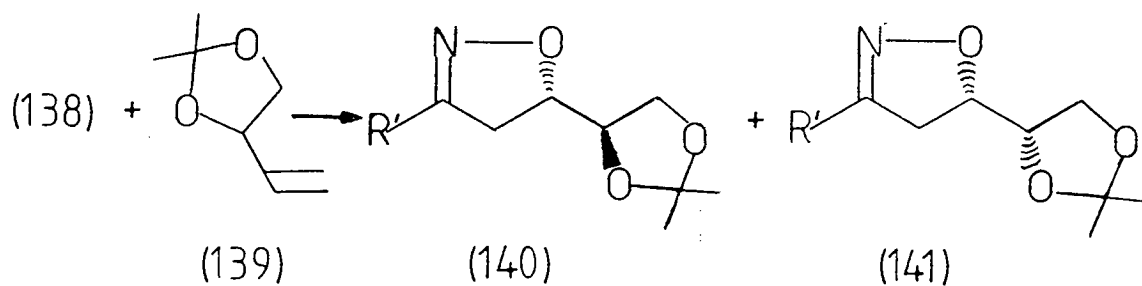


Scheme 24

The cycloaddition reactions of nitrile oxide with terminal alkenes whose allylic substituents differ by size (132) favours the formation of diastereomer (133) over (134). The magnitude of this preference depends on the relative sizes of the medium (M) and (L) groups ($S=H$) and ranges from negligible ($M=Me, L=Et; 1:1$) to modest ($M=Me, L=t-Bu, 4:1$).

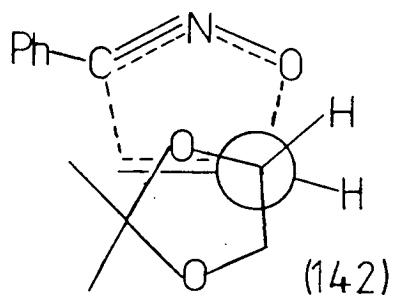
The important subset of reactions where the medium group is alkoxy (alkene 135) follows the same trend, although with improved stereoselectivity. For synthetically useful R groups, the anti diastereomer (136) typically predominates over the syn diastereomer (137) by a ratio of about 3:1. When $R=t-Bu$, the anti isomer is formed almost exclusively (15:1). The anti/syn ratio in these cycloadditions varies remarkably little with steric or electronic changes in either the nitrile oxide substituent (R') or the oxygen substituent (R''). The transition model(s) of Houk has successfully interpreted these trends (see page 53 of this thesis).

Jager and co-workers¹³⁸ in their concept to use the isoxazoline route for the synthesis of amino sugars reacted a variety of but-3-ene-1,2-diol derivatives with benzonitrile oxide and found that in all cases the formation of the anti cyclo adduct was favoured i.e. the cycloaddition had occurred preferentially on the face of the alkene that is more sterically shielded in the ground state. The highest anti : syn (140):(141) ratio was 85:15 for the cycloaddition of benzonitrile oxide (138) $R=Ph$ to (+)-(S)-Isopropylidenebut-3-ene-1,2-diol (139) Scheme 25.



Scheme 25

Jager rationalised the stereoselectivity using the Houk model, the favoured transition structure is shown in (142).



Kozikowski and Ghosh⁽¹⁰⁹⁾ also used the alkene (139) for their study, reacting it with a variety of nitrile oxides with varying degrees of selectivity (Table 2).

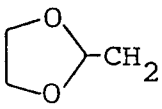
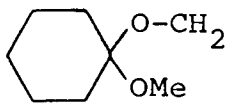
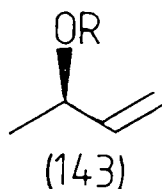
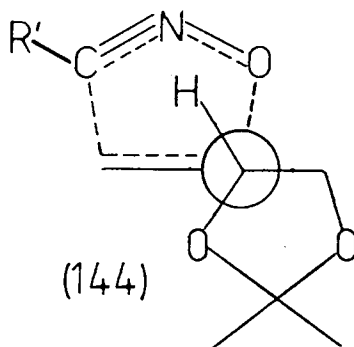
(138) R' =	anti:syn ratio (140):(141)
Me	88:12
Et	90:10
Ph	83:17
CO ₂ Et	80:20
CH ₂ OTHP	>94:<6
	80:20
	>94:<6

Table 2

Again in all cases, the anti product was favoured. They also studied the cycloaddition of the nitrile oxides in Table 2 with but-3-en-2-ol derivatives (143) R=TBDMS, CH₂Ph,

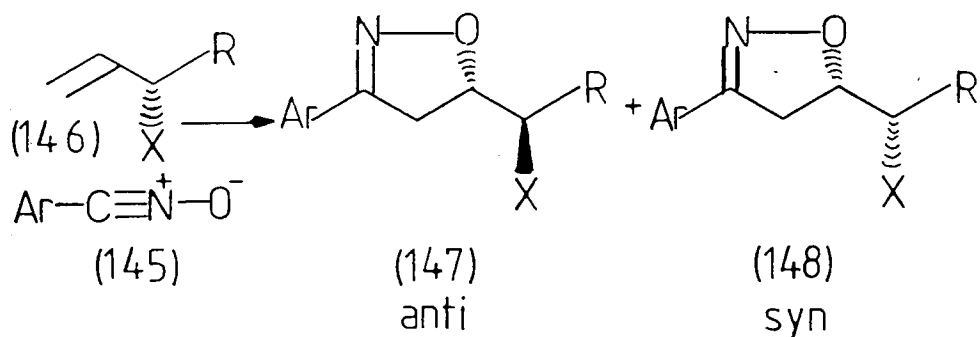


TBDPS, Ac and found again that the anti cycloadduct was favoured although the stereoselectivity of the reaction was lower. The stereoselectivity of the reactions was rationalised by Kozikowski by proposing a model (144) with the allylic alkoxy group aligned antiperiplanar to the forming CO bond in the transition structure.



Although the transition structure (144) is different to that proposed by Jager, model (142), both models favour the anti cycloadduct.

However Houk¹²⁶ was the first to combine experimental results with theoretical studies, and rationalised the stereoselectivity using various computational tests. Thus, his theory predicts that the diastereomeric preferences result from a transition structure similar to (142), in other words the cycloaddition will occur preferentially on the face of the alkene that is more sterically shielded in the ground state. The preference for this transition structure (149) was borne out in his experimental work (Scheme 26).



Scheme 26

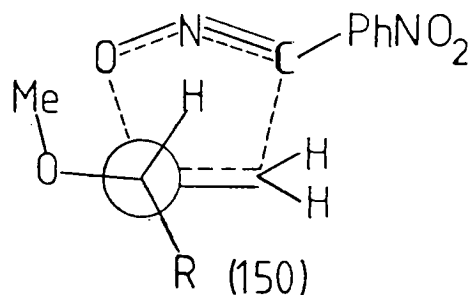
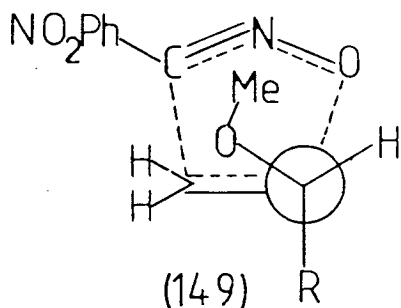
When R in (146) $x = \text{OSiMe}_2\text{Ph}$ increases in size, the diastereoselectivity favours the anti cycloadduct (147) (Table 3).

(146) x = OSiMe ₂ Ph, R=	Anti:Syn (147):(148)
Me	65:35
Et	80:20
<u>i</u> -Pr	91:9
<u>t</u> -Bu [†]	>95:<5

Table 3

His theoretical work predicts that the diastereomeric preferences observed in cycloadditions to chiral allyl ethers result from the alkoxy group's preference for the 'inside' conformation (see page 56 of this thesis) and the alkyl group's (R) preference for the anti position, leading to the favoured anti cycloadduct (147).

The minor syn cycloadduct results from the second best transition structure (150) i.e. the cycloaddition occurs preferentially on the face of the alkene that is least shielded in the ground state because it permits both the alkyl group and the alkoxy group to rotate slightly to a more relaxed conformation without increasing the repulsion effects of the two groups with the nitrile oxide oxygen.



As R increases in size beyond Me, the preference for transition structure (149) increases over transition structure (150), the C=CCR dihedral angle is large and in (150) the OMe

has an unfavourable conformation near the nitrile oxide oxygen and away from the alkene plane. Houk further concluded that the size of the alkoxy substituent has little effect of the stereoselectivity of the reaction.

Acyclic allylic alcohols were found to favour the syn cycloaddition with low stereoselectivities. Houk suggests that the OH group preferred the 'outside' position enabling hydrogen bonding between the OH group and the incoming nitrile oxide oxygen. The product ratios were found to be solvent dependent ranging from anti:syn ratio of 40:60 in ether to 60:40 in DMF. This seems to confirm Houk's explanation as hydrogen bonding between the allylic alcohol and the solvent eliminates the hydrogen bonding between the reactants in the transition state, resulting in ratios nearly identical with those found for the corresponding allylic ether.

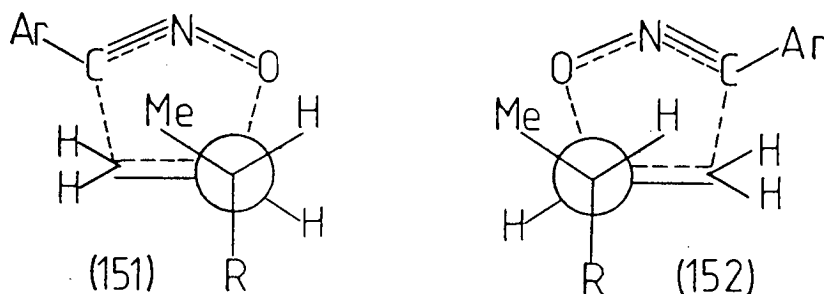
In a later report Houk¹²⁴ studied the cycloaddition of (145), $\text{Ar}=\text{NO}_2\text{Ph}$, with various 3-substituted but-1-enes (146), $\text{X}=\text{Me}$ to give the diastereomers (147), $\text{X}=\text{Me}$ and (148) $\text{X}=\text{Me}$ in Scheme 26.

In every case the major product was the anti cycloadduct (147) i.e. the cycloaddition had occurred preferentially on the face of the alkene that is more sterically shielded in the ground state. It was also noted that as the size of the R group increased, the reaction became more stereoselective (Table 4).

(146) X=Me, R=	Anti:Syn (147):(148)
Et	50:50
Ph	59:41
<u>i</u> -Pr	65:35
<u>t</u> -Bu ^t	77:23

Table 4

Houk's computational calculations showed that the major anti cycloadduct arises from the transition structure (151) and the minor syn cycloadduct from transition structure (152).

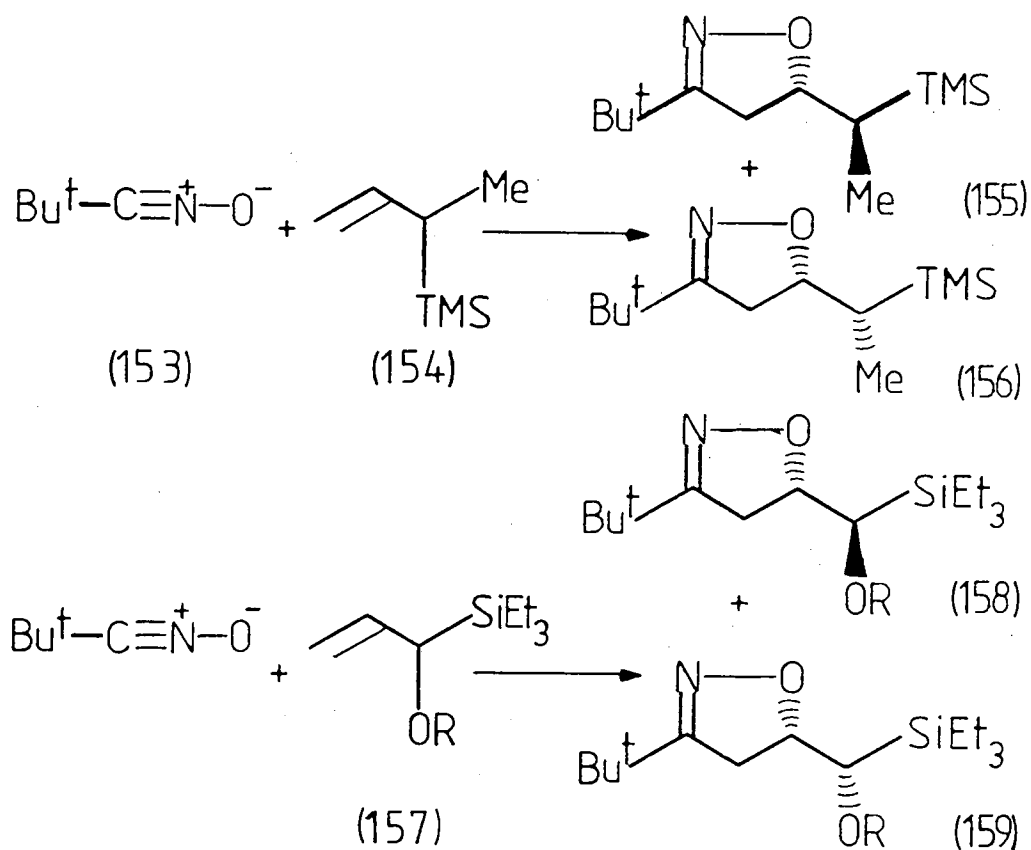


The transition structure (151) can simultaneously avoid methyl(inside)-O(nitrile oxide) and R(anti)-CH₂ repulsions, unlike (152) with its methyl(outside)-O(nitrile oxide) and R(anti)-CH₂ repulsion competing against one another. Thus (152) is the less stable transition structure, which is further destabilised when the size of the anti group increases thus favouring the transition structure (151) more.

The preferred transition structure (151) is similar to the model for the nitrile oxide cycloaddition to allylic ethers (149) i.e. in both cases, the cycloaddition occurs preferentially on the face of the alkene that is more sterically shielded in the ground state.

Houk concluded that these conformational preferences appear to be dominated by steric effects, unless a heteroatom is present in the allylic chiral center. When a heteroatom such as oxygen is present in the allylic chiral centre, the conformational preferences are dominated largely by electronic factors.

Curran and Gothe have studied the cycloaddition of nitrile oxide (153) with α -chiral butenyl silanes (154) and chiral (α -oxyallyl) silanes (157) in Scheme 27.



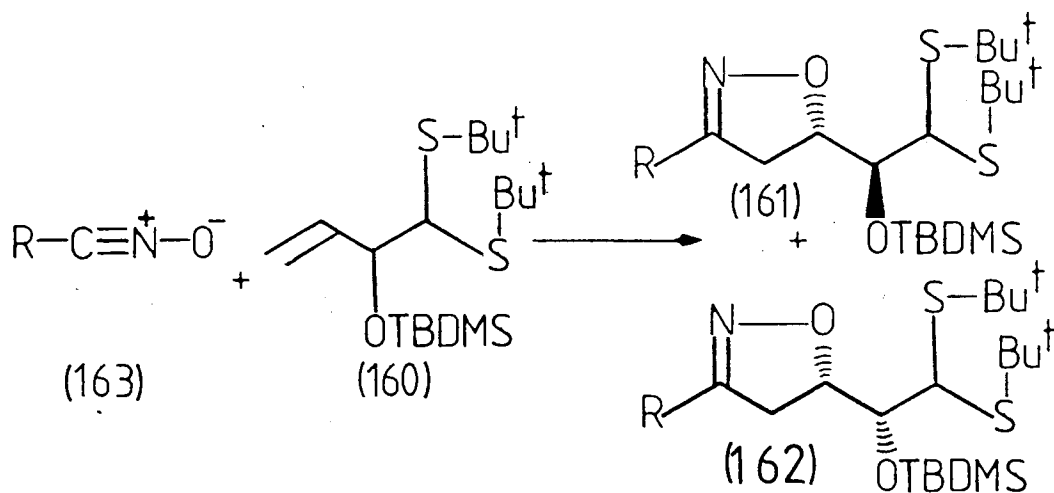
Scheme 27

In the case of (154) Curran¹³⁹ had assumed that the trimethylsilyl group of a chiral allylic silane should show a healthy preference for the anti position for both steric and electronic reasons (to maximise electron donation), however the diastereoselectivities were quite low although the major product (155) was that predicted by the Houk model

(151) $R=SiEt_3$.

In the case of the chiral (α -Oxyallyl) silanes (157) Curran¹⁴⁰ found that the anti isomer (158) was favoured for the same reasons as discussed previously, but the silyl derivative was found to be less selective than its tert-butyl counterpart and about the same as iso-propyl, although no explanation was given.

Cozzi and his co-workers¹⁴¹ have studied the nitrile oxide cycloaddition to alkylethers derived from 1,1-dithio-3-buten-2-ols (160) (Scheme 28). Their aim was to use the high diastereoselectivity found in the nitrile oxide cycloaddition, which would afford products amenable to further synthetic elaboration.

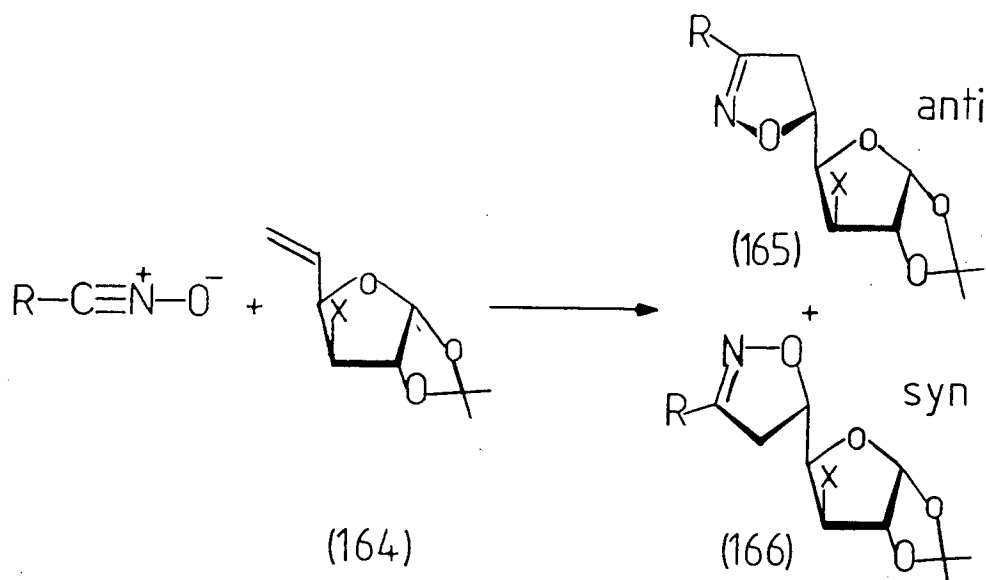


Scheme 28

They found that the stereoselectivity was high >89:11, irrespective of the nitrile oxide used (163)

$R = \text{Me}, \text{Ph}, \text{CO}_2\text{Et}, \text{pMeOC}_6\text{H}_4, \text{CH}_2\text{OCH}_2\text{Ph}, 2\text{-thiazoloyl}$, although some cycloadducts were obtained in low yields. The major isomer was found to be the anti isomer (161) again rationalized in terms of Houk's proposed transition structure (149) ruled by the "inside alkoxy effect".

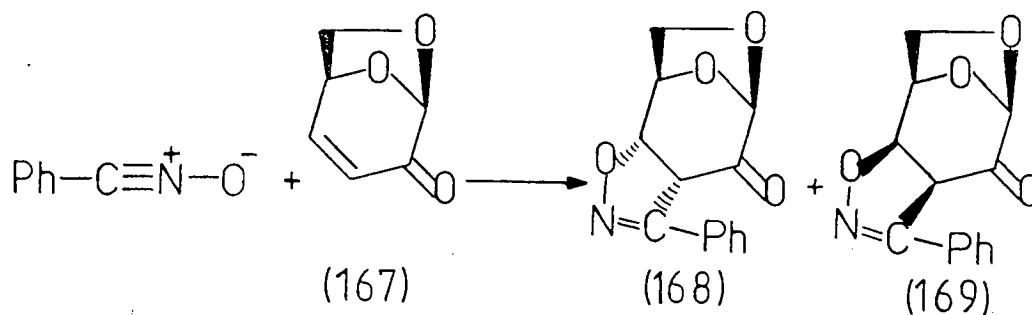
Micheli, Gandolfi, Toma and co-workers¹⁴² have reported the nitrile oxide cycloaddition to unsaturated sugars (164) to give the anti adduct (165) with 74-97% stereoselectivity in high yields (Scheme 29) .



Scheme 29

The minimum energy conformations of the dipolarophiles and the relative energies of model transition structures were evaluated by MM2 calculations; their results confirming the model proposed by Houk.

Regio- and face-selectivity has been reported¹⁴³ in the benzonitrile oxide cycloaddition to levoglucosenone (167). The major cycloadduct (168) in 71% yield is generated by a lower face attack by the nitrile oxide. Due to the rigid configuration of levoglucosenone, the upper face approach is hindered giving the minor product (169) in 0.6% yield.



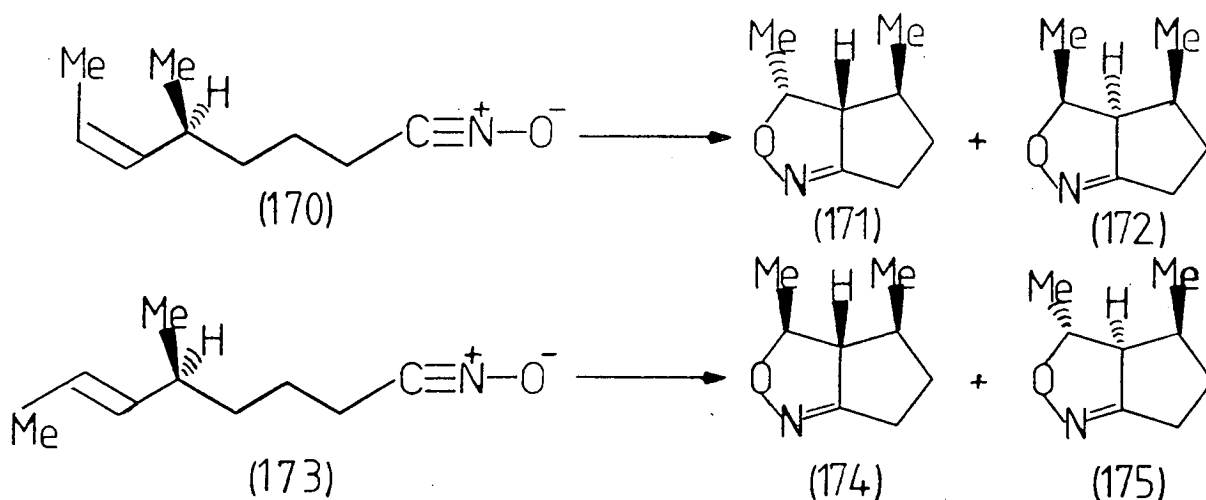
Scheme 30

Despite the impressive amount of research on nitrile oxide cycloaddition to allylic chiral alkenes, the influence of double bond configuration on the stereochemical outcome of the cycloaddition reaction has been studied only to a limited extent^{109,144} probably because of the poor regioselectivity observed for the cycloaddition to unsymmetric disubstituted alkenes.

However the use of intramolecular nitrile oxide cycloaddition reactions allows an evaluation of the effect of alkene geometry.

Intramolecular nitrile oxide cycloaddition

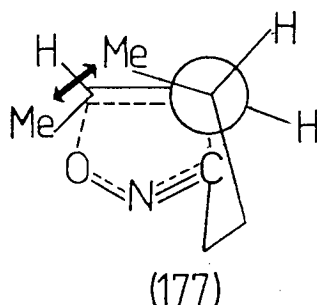
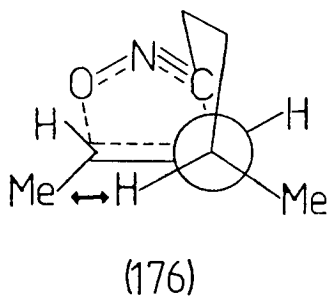
Kozikowski and Chen¹⁴⁵ in 1982 reported the first intramolecular nitrile oxide cycloaddition to an alkylic chiral alkene. However, the chiral centre was located within the carbon chain connecting the dipole and dipolarophile and therefore any comparison with their intermolecular counterparts will be invalid (Scheme 31).



Scheme 31

In the case of the *Z*-alkene (170) only a single isoxazoline (171) at >98% purity was isolated.

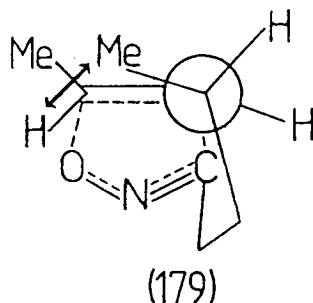
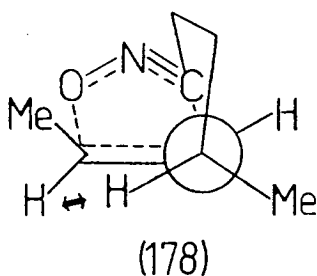
The favoured transition structure leading to cycloadduct (171) was postulated as being (176), in which the conformation involves only a methyl-hydrogen interaction (\longleftrightarrow).



The transition structure (177) leading to the other possible isomer (172), involves a methyl-methyl interaction (\leftrightarrow), which is so severe that it prevents the formation of the cycloadduct.

The intramolecular cycloaddition of the E-alkene (173) gave a 3:1 mixture of two cycloadducts (174):(175) respectively.

In the two favoured transition structures (178) and (179), a methyl-hydrogen interaction is present in (179), whereas a less serious hydrogen-hydrogen interaction is found in (178). Since these steric interactions are much less serious than a methyl-methyl interaction, the cycloaddition reaction was expected to be less discriminating in its preference for the cycloadducts.



Subsequent studies have concentrated on alkenes with an allylic chiral centre which is not part of the link between the dipole and dipolarophile.

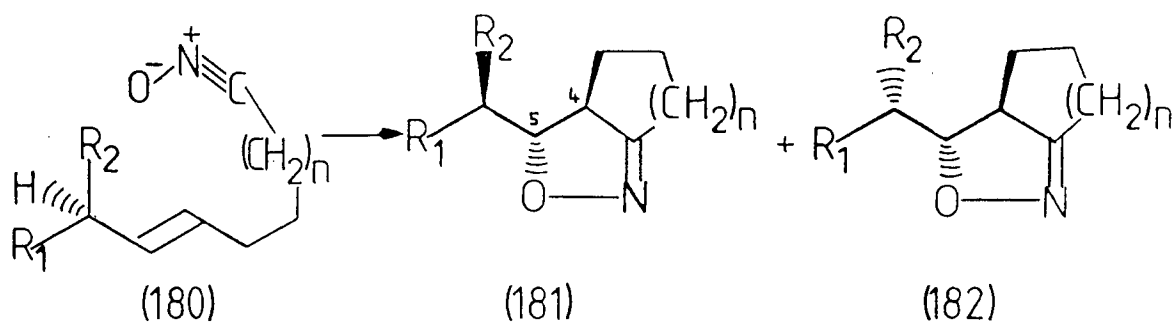
Cozzi and Gennari and their co-workers¹⁴⁶ have recently reported their work on the stereoselectivity found in intramolecular nitrile oxide cycloadditions to allylic chiral alkenes and have rationalised their results with transition structure models derived from MM2 calculations (performed on the updated version MODEL). Their studies concentrated on E- and Z-chiral alkoxy alkenes, E- and Z-chiral allylic alkenes (no heteroatom in the chiral group) and the effect of varying the length of the carbon chain linking the dipoles and dipolarophile. (An earlier report by Cinquini and Cozzi¹⁴⁷ discusses the stereoselectivities found using E- and Z-alkenyl nitrile oxides containing a sulphur atom in the linking chain. Similar stereoselectivities were found to the results discussed below).

In the synthesis of the cycloadducts, yields were generally good for cyclohexane forming reactions for example (181) $n=2$ in Scheme 32, while lower yields were found for the cyclopentane forming reactions for example (181) $n=1$. The stereoselectivity of the latter was also found to be lower than their cyclohexane forming counterparts. Both the low yield and the low stereoselectivity, are probably a result of the difficulty for the nitrile oxide and the alkene to reach the geometry required by the transition state. The cycloaddition reaction retains the stereochemistry of the alkene, thus from Z-alkenyl nitrile oxides C-4/C-5 syn and from

E-alkenyl nitrile oxides C4/C-5 anti products were obtained, respectively.

In the nitrile oxide cycloaddition of all the chiral alkenes, the anti cycloadduct predominates.

In the cycloaddition of the E-chiral alkoxy alkenes (Scheme 32) good stereoselectivities were found (Table 5).



Scheme 32

R_1	(180) R_2	$n=$	Anti:Syn (181):(182)
OCH_2Ph	Me	2	60:40
OCH_2Ph	CH_2O CH_2Ph	2	77:23
$OC(CH_2)_5OCH_2$		2	86:14
$OC(CH_2)_5OCH_2$		1	78:22
OCH_2Ph	Me	1	58:42
<u>i</u> -Pr	Me	2	66:34

Table 5

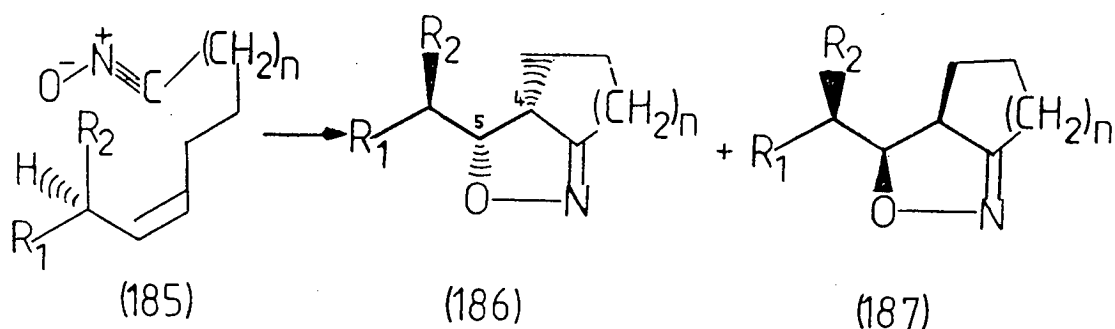
The extent of the diastereoselectivity closely parallels those of the intermolecular reaction using monosubstituted alkenes, and Cozzi and Gennari predicted that the same model as used by Houk would apply. Their MM2 calculations agreed with Houk's postulate of staggering in the transition structures. They concluded that the preferred transition structure was (183) for the major anti cycloadduct and (184) for the minor syn cycloadduct.



Transition structure (183) is preferred over (184) due to the electronic factors discussed previously (see page 56 of this thesis).

For non heteroatom chiral allylic alkenes (Scheme 32, $R_1 = iPr$, $R_2 = Me$) the above transition structures (183) and (184) again both dominate. Conformation (183) with the medium sized group (Me) inside is favoured over (184) having (Me) outside, because of the repulsion between the outside Me group and the incoming nitrile oxide oxygen.

In the nitrile oxide cycloaddition of the Z-chiral alkoxy alkenes and non heteroatom allyl alkenes (Scheme 33) the stereoselectivities (Table 6) were found to be higher than their E-alkene counterparts.



Scheme 33

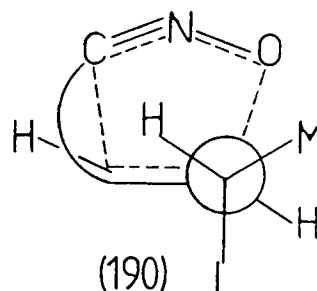
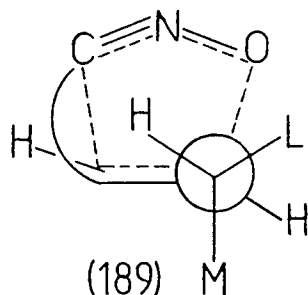
(185)		n	Anti:Syn (186):(187)
R_1	R_2		
OCH_2Ph	Me	2	80:20
OCH_2Ph	$\text{CH}_2\text{OCH}_2\text{Ph}$	2	83:17
$\text{OC}(\text{CH}_2)_5\text{OCH}_2$		2	86:14
$\text{OC}(\text{CH}_2)_5\text{OCH}_2$		1	75:25
OCH_2Ph	Me	1	81:19
$i\text{-Pr}$	Me	2	66:34

Table 6

To rationalise the stereoselectivities found Cozzi and Gennari predicted that the Houk model would not apply as the presence of substituents cis to the allylic carbon would disfavour the inside position for the medium sized substituent due to steric crowding.

Their MM2 calculations confirmed this hypothesis and they

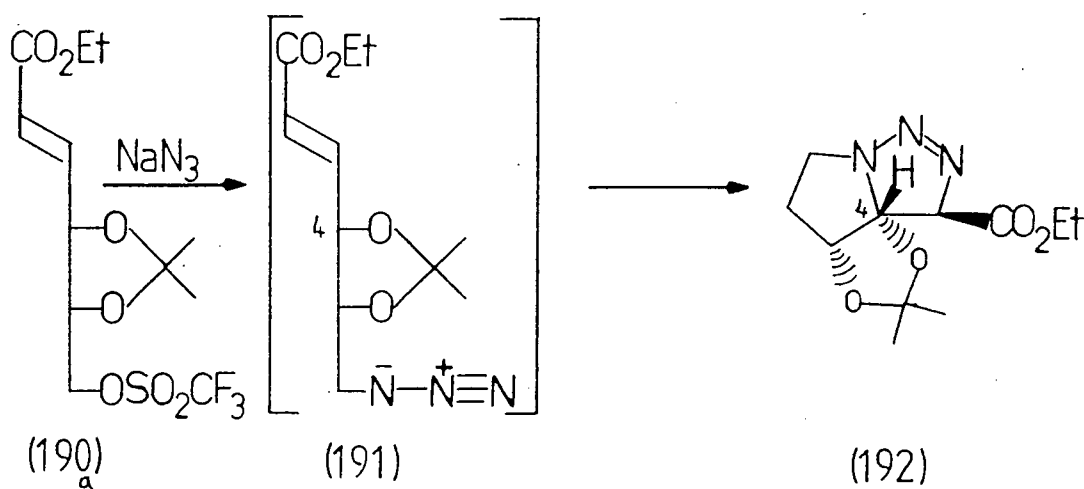
proposed a new model for the intramolecular nitrile oxide cycloaddition to Z-alkenes. They proposed that the preferred transition structure was (189) for the major anti cycloadduct and (190) for the minor syn cycloadduct.



In both cases the most crowded position is preferentially occupied by the small group (H). Transition structure (189) is preferred to (190) because the cis-CH₂/medium (anti) interaction is smaller than the cis-CH₂/large (anti) interaction suffered by (190). This steric effect is so significant that it overwhelms electronic effects, such as the tendency for an allylic oxygen to occupy the inside position.

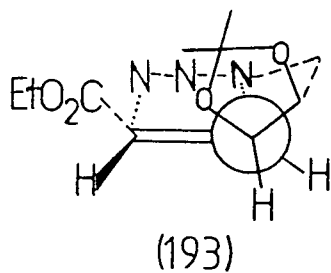
3.3.3) Azides

Buchanan and his co-workers¹⁴⁸ have reported in their synthesis of chiral pyrrolidines, an intramolecular 1,3-dipolar cycloaddition of an azide group to the attached (E)- α,β -unsaturated ester (190a) to give the dihydrotriazole (192) exclusively in 68% yield (Scheme 34).



Scheme 34

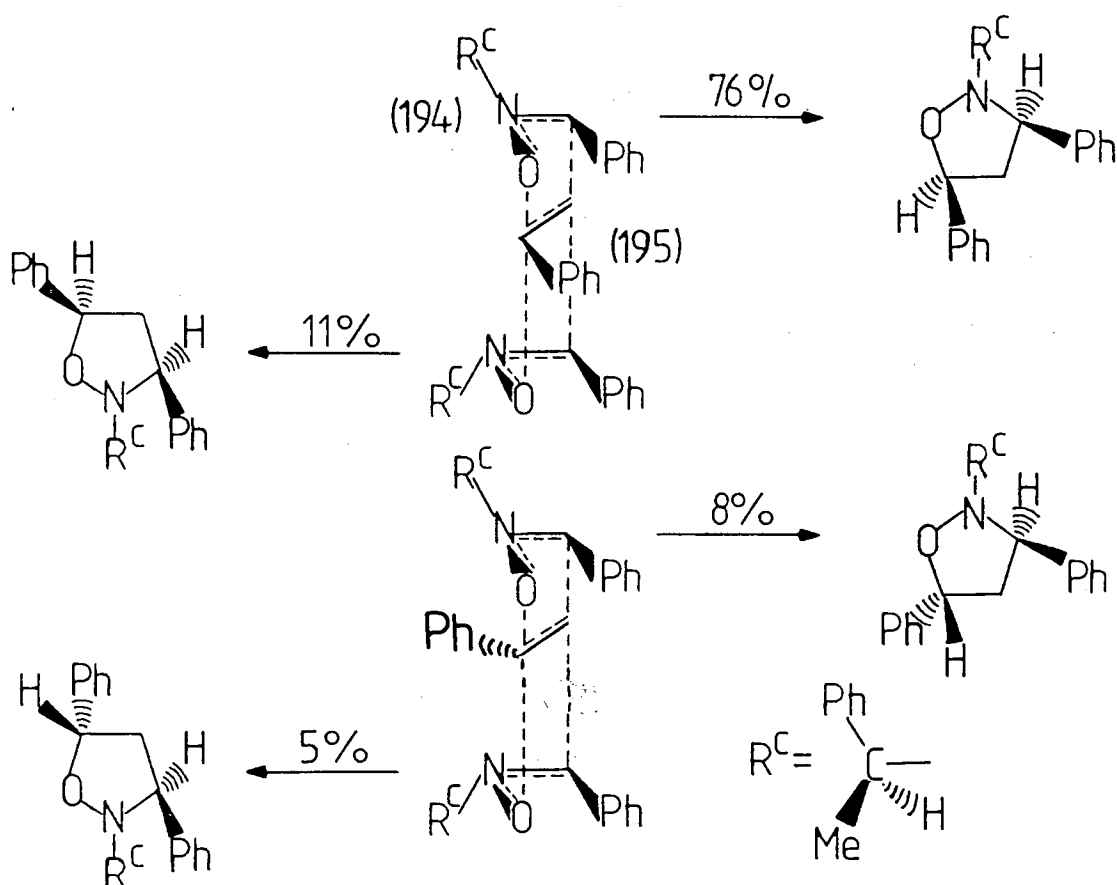
On examination of the possible conformations for the transition structure, Buchanan concluded that there appeared to be no steric preference for any of the possible conformations, but structure (193) is similar to Houk's 'inside' alkoxy model. As (193) is the transition structure which yields exclusively (192), the above hypothesis is reasonable.



3.3.4) Nitrones

The majority of reports published have employed a nitron with a chiral group attached to the nitrogen in the 1,3-dipole and a prochiral alkene.

Chiral nitrones such as (194) undergo cycloaddition with styrene (195) to give four possible isomers of the isoxazolidine¹⁴⁹. Scheme 35 summarises the transition structure responsible for each isomer.



Scheme 35

Other reports of chiral nitron cycloadditions are given in a recent paper¹⁵⁰.

Whitney¹⁵¹ has recently studied asymmetric induction of achiral nitrones with allylic chiral alkenes and has used computational methods to rationalise the work.

DISCUSSION

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[* - R^C refers to Scheme 2, page 83]

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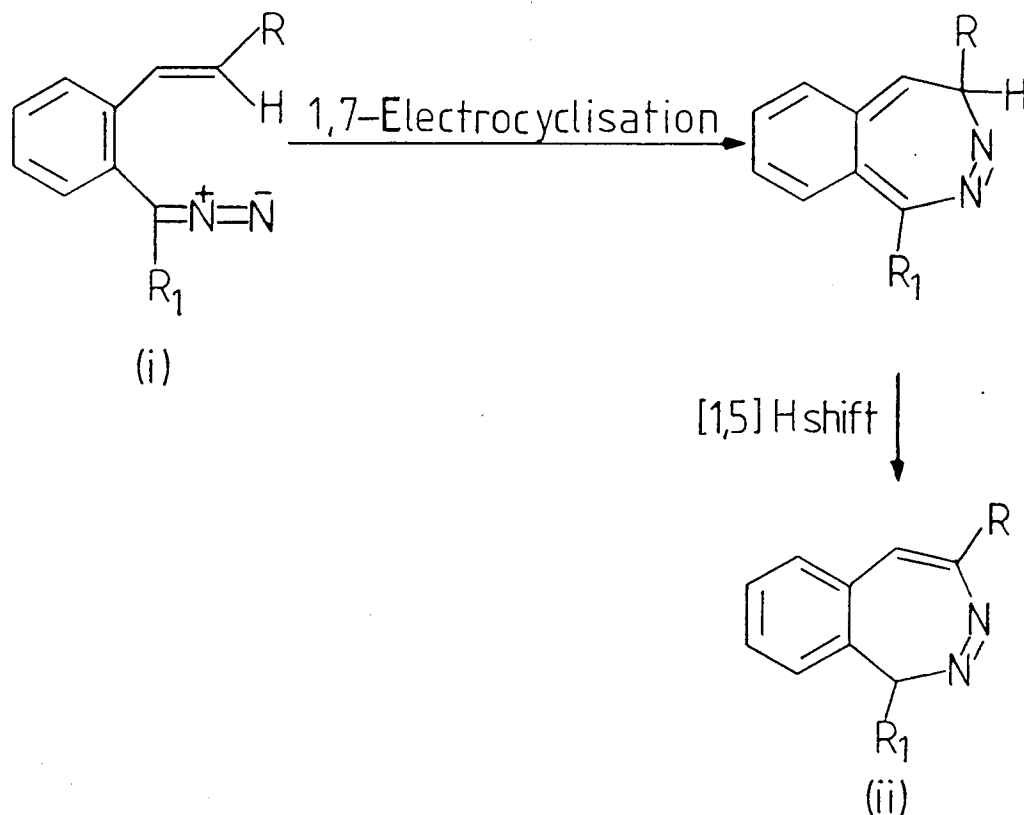
SECTION 2

EXPLANATION OF THE STEREOSELECTIVITY FOUND IN THE 1,7-ELECTROCYCLISATION REACTION.

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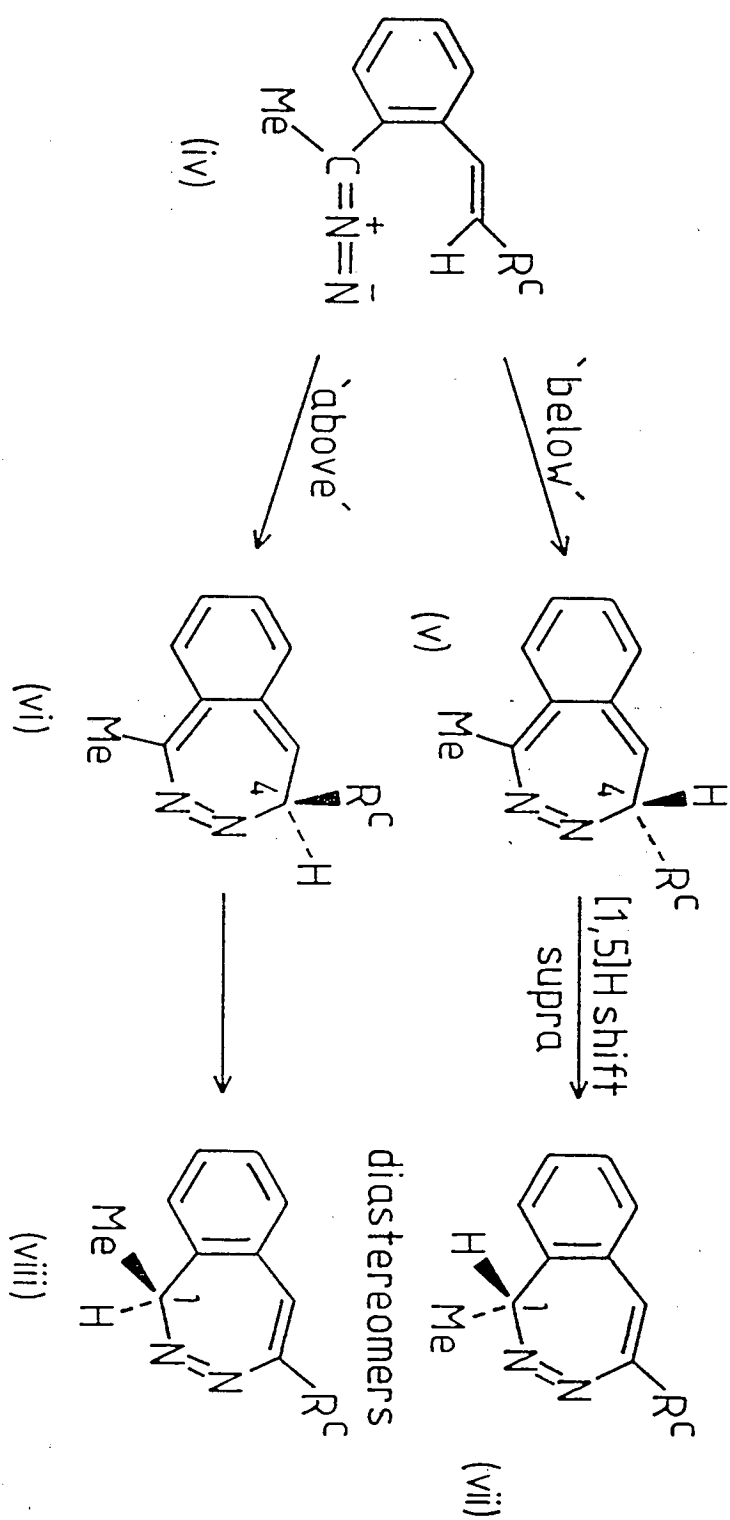
DISCUSSIONPREAMBLE

It has been known for some time that $\alpha, \beta:\gamma, \delta$ -unsaturated diazoalkanes, having α, β -aromatic unsaturation, (i) undergo a cyclisation to give, for example, 1H-2,3-benzodiazepines (ii) as shown in Scheme 1.

Scheme 1

It is thought that this conversion involves two steps, firstly, a 1,7-electrocyclisation, and secondly, an intramolecular sigmatropic [1,5] hydrogen shift.

The object of this research was to discover the effect on the course of the reaction produced by a chiral substituent R^C sited at the olefinic terminus of the conjugated system (Scheme 2).

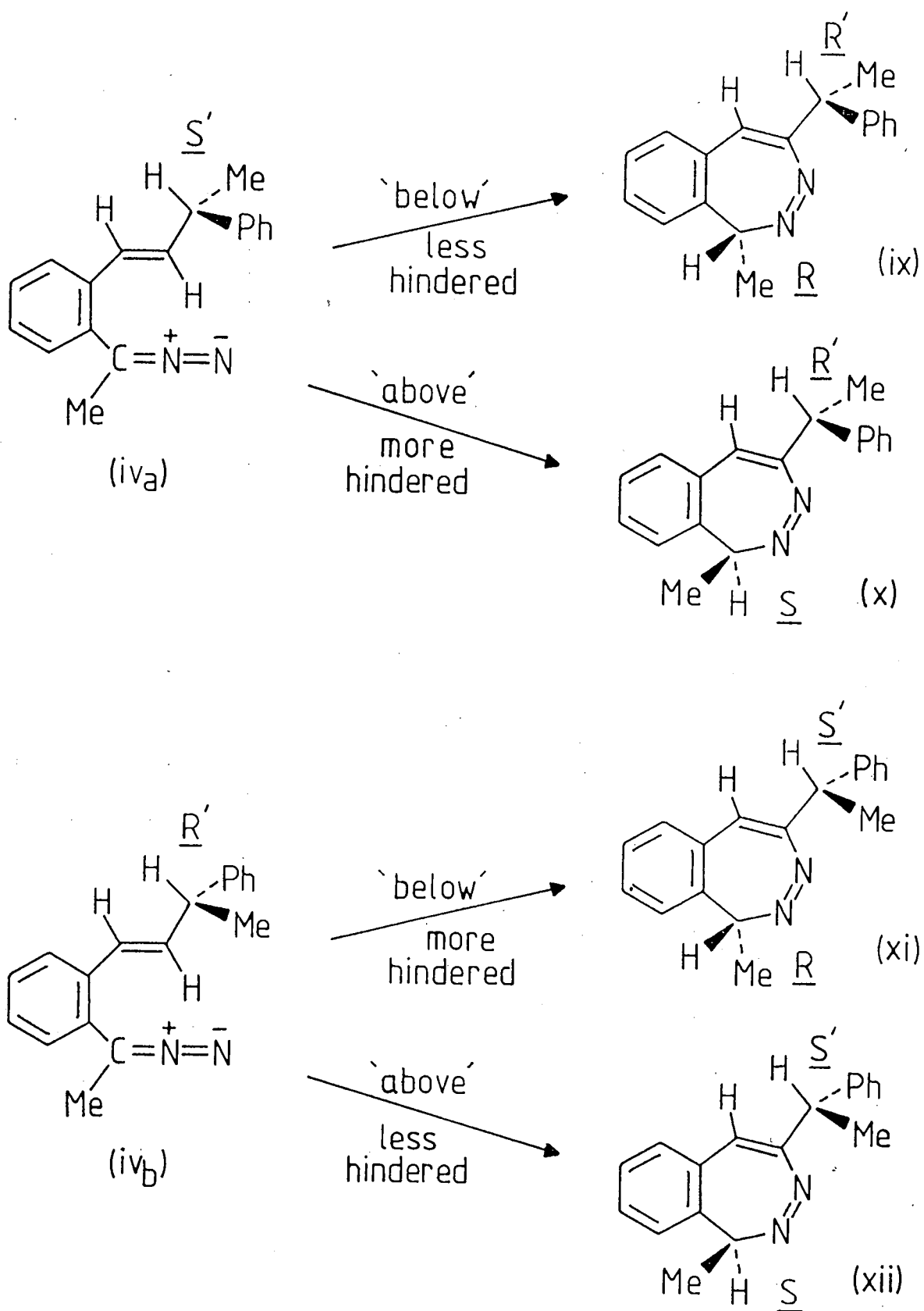


Scheme 2

Cyclisation of (iv) can occur via approach of the terminal nitrogen to either face of the double bond, so producing as the primary products a pair of diastereomers (v and vi) which have a new chiral centre at C-4 adjacent to R^C. The suprafacial hydrogen migration in the second step will then transfer the chirality at C-4 stereospecifically to C-1 to produce the product pair of diastereomers (vii and viii) which have the new chiral centre at C-1.

In almost all cases the cyclisations were carried out using racemic diazo-compounds. The use of racemates rather than single enantiomers much simplified the effectiveness of the study in determining the effect of the chiral group on the course of the cyclisation. It is however worth noting at this point that several of the syntheses used for the precursors could easily be adopted to produce single enantiomers (or at least very highly enriched mixtures) by using the highly specific carbonyl reduction technique recently developed by Corey ¹⁵².

In the example shown in Scheme 3, the products from each enantiomer of the diazoalkane are shown. Cyclisation of (iva) will produce the pair of diastereomers (ix) and (x) in a ratio dependent on the effect of the chiral group in inducing "above/below" face selectivity. Similarly the other enantiomer (ivb) will produce the diastereomers (xii) and (xi) in an identical ratio. The transition state for the formation of (xii) will be of identical energy to that for the formation of (ix) (mirror images), and that for (x) the same as for (xi). The enantiomers (ix) and (xii) will therefore be produced in equal amounts and likewise for (x) and (xi). The product



Scheme 3

mixture will thus be optically neutral but the diastereomer ratio of (ix) and (xii) to (x) and (xi) will depart from [1:1] if the chiral group in (iv) is effective in inducing face selectivity.

The following Sections 1.1 to 1.9 deal with the synthetic route followed to the tosylhydrazone precursor of each diazo-compound, its cyclisation and the measurement of the diastereomer ratio. In each case, this is followed by a brief comment on the structure of the major product and its relationship to the preferred ground state conformation of its precursor. The results are summarised in Section 1.10 on page 127 and the full discussion and rationalisation of the observed stereoselectivity is presented in Section 2.

Section 1. Synthesis and Cyclisation Reactions of the Chiral Diazocompounds.

1.1. $R^C = 1\text{-Phenylethyl}^*$.

1.1.1. Synthesis of the Chiral Tosylhydrazone Precursors.

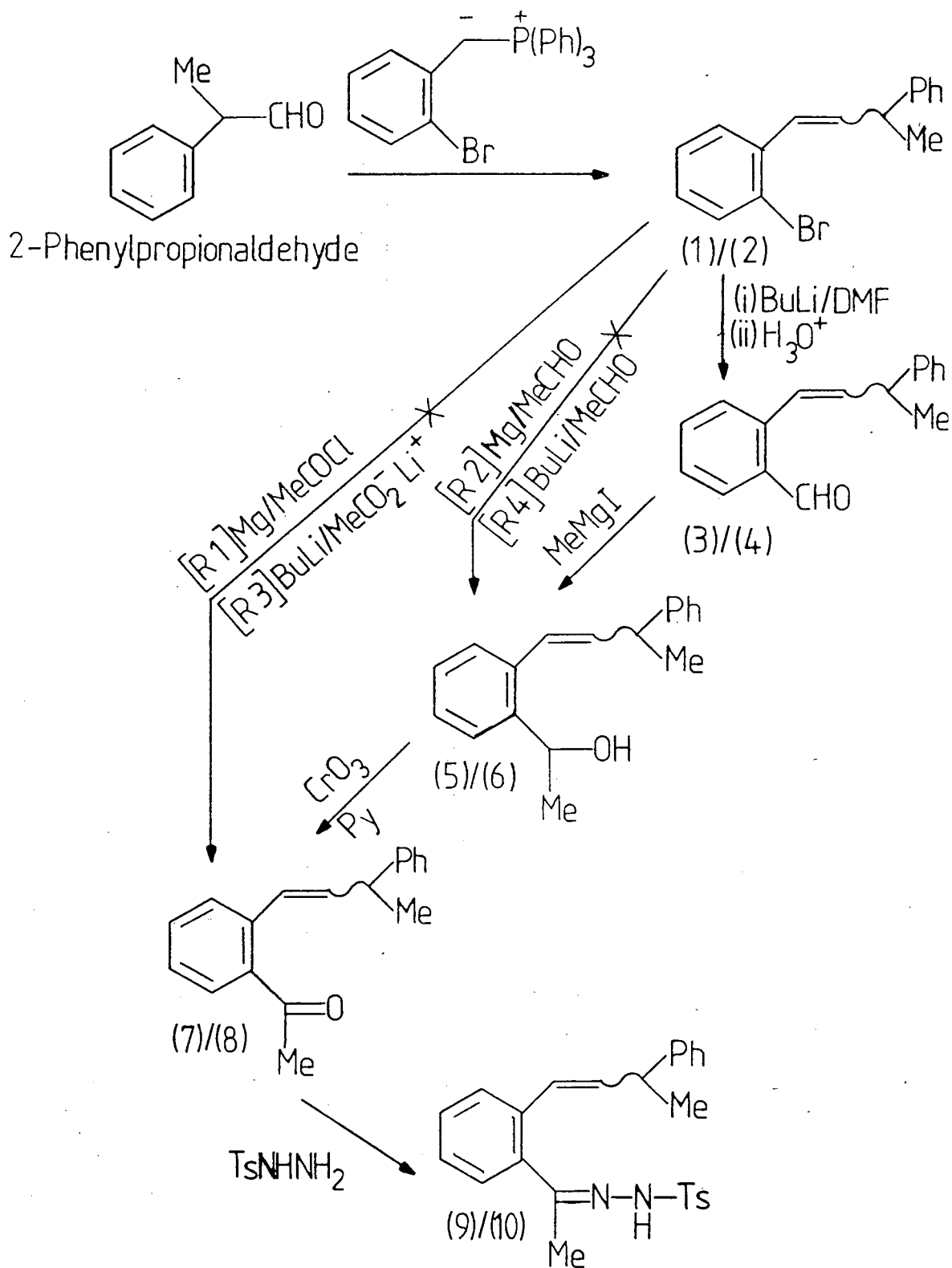
The first target was the ketone (7) in Scheme 4. This was chosen because the chiral centre could be placed in the required position by the use of the readily available 2-phenylpropionaldehyde. This chiral centre has also been shown to induce stereoselectivity in nucleophilic and in cycloaddition reactions⁹⁴.

A Wittig reaction of 2-phenylpropionaldehyde with the ylide, generated from 2-bromobenzyltriphenylphosphonium bromide and sodium ethoxide, gave a mixture of E- and Z-isomers (1) and (2) respectively, in high yield. Attempts to remove the Z-isomer (2) by chromatography, or by isomerisation using iodine in boiling heptane failed. It was decided to proceed using the E/Z-mixture in the hope that the isomers would be separable at some later stage in the synthesis.

A one step synthesis of ketones (7)/(8) was attempted ([R1] in Scheme 4) using a Grignard reagent prepared from the E/Z mixture (1)/(2) and to it was added acetyl chloride at -78°C . A multicomponent mixture was formed, none of which were identified as being the required ketones.

A reaction between the above Grignard reagent and acetaldehyde was then tried in an attempt to synthesize the

[* $-R^C$ refers to Scheme 2, page 83]



Scheme 4

alcohols (5)/(6) ([R2] in Scheme 4). A multicomponent mixture was obtained, containing only 6% of the alcohols (5)/(6).

The experiments above suggest that the intermediates under the reaction conditions are unstable and therefore, it was decided to use an alternative approach via the use of organolithium reagents. To test that the organolithium reagent is formed, the compounds (1)/(2) were reacted with butyllithium at -78°C , and then quenched with water. G.l.c. analysis showed that two products were formed. These were identified by ^1H n.m.r. as beeing the E-and Z-isomers of phenylbut-1-enylbenzene (11)/(12); confirming that a lithium-halogen exchange had occured, generating the required organolithium reagent.

A one step synthesis of the ketones (7)/(8) was attempted by the reaction of the organolithium reagent of (1)/(2), with lithium acetate at -78°C in a method described by Rubottom¹⁵³ ([R3] in Scheme 4). G.l.c. analysis indicated that the major product was the mixture of unsaturated hydrocarbons (11)/(12).

A reaction between the above organolithium reagent and acetaldehyde was then tried in an attempt to synthesize the alcohols (5)/(6) ([R4] in Scheme 4). T.l.c. indicated that the crude product contained the alcohols; but to avoid losses by isolation, the crude alcohols were converted to the ketones (7)/(8) by a Jones oxidation and then the ketones were isolated. However the yield of ketones was very low.

Earlier co-workers had successfully used the reaction between organolithium derivatives and dimethylformamide at -78°C , followed by hydrolysis to give similar aromatic aldehydes. Consequently, the organolithium reagent of (1)/(2)

was generated and dry dimethylformamide added. Hydrolysis gave the aldehydes (3)/(4) in good yield. Addition of a methylmagnesium iodide reagent to the aldehydes (3)/(4) gave the required alcohols (5)/(6) in high yield; Jones oxidation was then used to give the ketones (7)/(8). The ketones (7)/(8) were converted by condensation with *p*-toluenesulphonylhydrazide under mild conditions to give a mixture of syn and anti isomers of the *p*-toluenesulphonylhydrazones (9)/(10). Separation of the syn (10) and anti (9) isomers was achieved by chromatography. However, separation of the E- and Z-isomers could not be achieved in any of the above steps.

While the above work was being carried out, it was observed that the E- and Z-mixture of isomers of the bromoalkene (1)/(2) had partially crystallised in a freezer. On investigation, it was discovered that only the Z-isomer (2) had crystallised. Subsequently, it was found that removal of most of compound (2) from the mixture could be achieved by crystallisation from cold petrol. Careful fractional distillation removed the remaining 10%. The pure E-isomer (1) obtained was used to prepare the E-ketone (7) using the procedure described above. The E-ketone (7) was converted by condensation with tosylhydrazide to the syn- and anti-tosylhydrazones (14)/(15).

The overall yield from the conversion of the (1) to the tosylhydrazones (14)/(15) was 10%.

1.1.2. Decomposition of the Tosylhydrazone Sodium Salts.

The tosylhydrazones (9) and (14)/(15) were used to generate the required diazo-compounds via the Bamford-Stevens

reaction⁴⁸.

Conversion of the tosylhydrazones to the sodium salts was carried out by stirring at room temperature in 'super-dry' ethanol containing 0.95 molar equivalents of sodium ethoxide. A deficiency of base was used so as not to cause any base catalysed isomerisation of the primary products. The decomposition of the tosylhydrazone salt was carried out in dry, boiling solvent for the minimum time required to consume all of the starting material. The products were isolated by filtering off the *p*-toluenesulphinate which had precipitated during the reaction, removing the solvent by evaporation under reduced pressure. The crude residue was then analysed for the ratio of diastereomers by ¹H n.m.r. and by h.p.l.c. as discussed below, and then finally separated by m.p.l.c. to give the pure diastereomers.

The first cyclisation was carried out in cyclohexane, using the mixed E/Z tosylhydrazones (9)/(10), obtained in the first synthesis. As expected from earlier work⁷⁸, the E-isomer cyclised to give a diastereomeric pair of benzodiazepines (67)/(69), while the Z-isomer gave carbene-derived products which were not examined further. All the succeeding work however was carried out using the pure E-isomer of the tosylhydrazone once it became available, and gave the benzodiazepines in high yield.

The crude products from the above reactions were combined and the diastereomers were separated by m.p.l.c..

Each diastereomer had similar physical characteristics to their non-chiral analogues⁷⁸. For example, the major isomer was a yellow crystalline solid, the mass spectra showed only a

small peak due to the parent ion, confirming that the structure had the formula $C_{18}H_{18}N_2$ and also a base peak of (P-28) was found, a characteristic of benzodiazepines, formed by the loss of a molecule of nitrogen.

Further confirmation of the structure of the isomers was achieved by comparison of their 1H n.m.r. and ^{13}C n.m.r. spectra with the spectra of known 1H-2,3-benzodiazepines⁷⁸. In each case, the 1H n.m.r. spectra showed the characteristic deshielding effect by the diazo-group of the C-1 hydrogen. For example, diastereomer (67) shows a high field absorption at 4.40 ppm, confirming the exo position of the C-1 hydrogen. Also, absorption by (67) at δ 6.32 ppm was similar to the C-5 hydrogen absorption of known 1H-2,3-benzodiazepines. The ^{13}C n.m.r. spectra further supported the structures of (67) and (69) to be that of 1H-2,3-benzodiazepines. The spectra of (67) showed a saturated carbon absorption at δ 71.0 ppm and a quaternary carbon absorption at δ 158.8 ppm. The absorption of the carbon atoms in these deshielded positions duplicated the absorption found for the C-1 carbon and the C-4 carbon of a reported 1H-2,3-benzodiazepine⁸⁰.

A crystallographic structure determination carried out on the major isomer confirmed its structure to be that of 1H-2,3-benzodiazepine and also determined the relative stereochemical configuration of the two chiral centres. The result is shown in structure (67) in Scheme 5 (see Appendix III, Picture 1). Therefore the relative stereochemical configuration of the minor product must be that of structure (69).

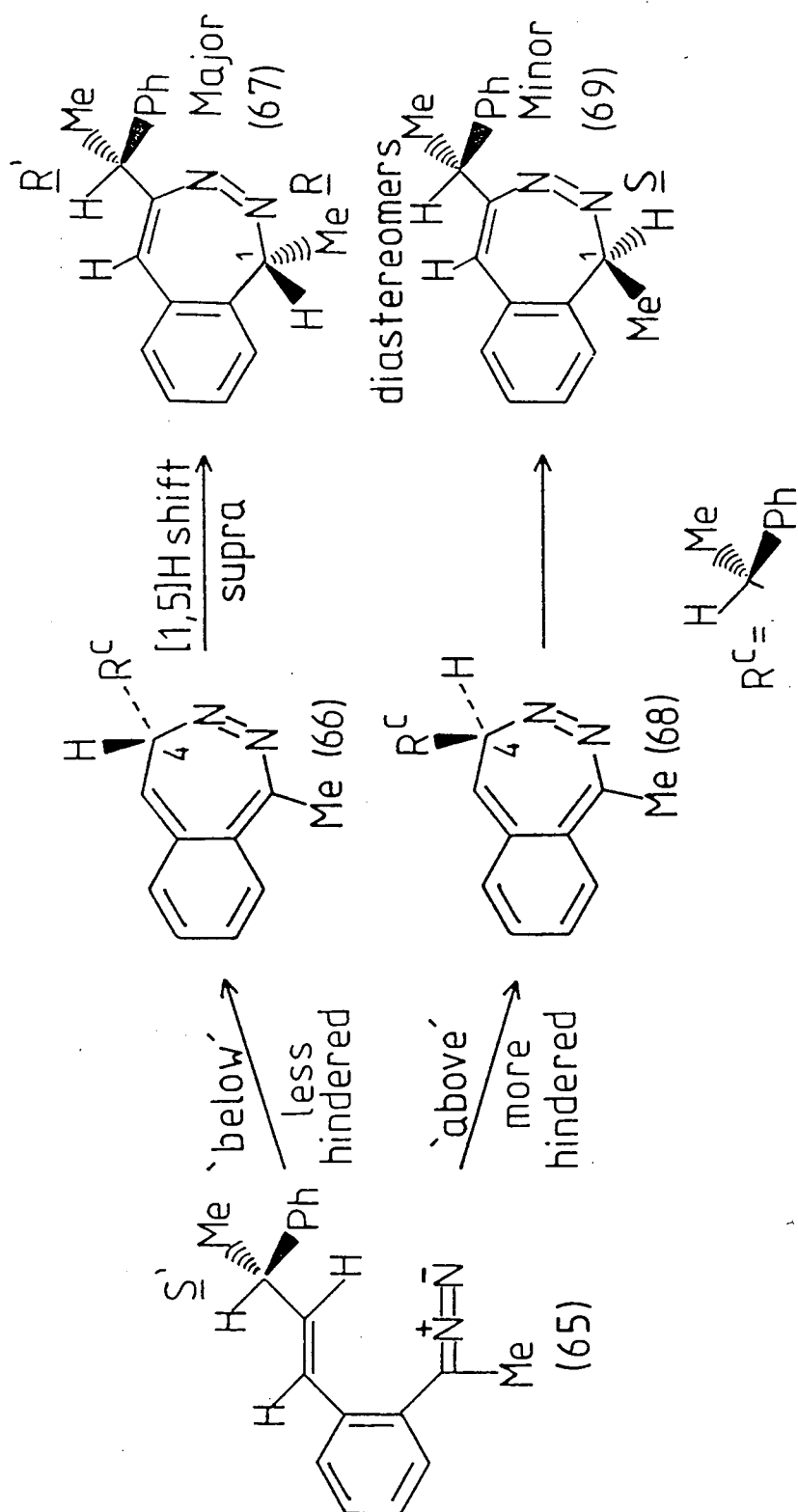
The ratio of the benzodiazepine diastereomers (67):(69) was measured by 1H n.m.r. using the integrals of the

C-5 hydrogens and confirmed by h.p.l.c. (see Appendix II, Diagram 1). The first cyclisation gave 54:46 (n.m.r.) and 53:47 (h.p.l.c.), while cyclisation of the pure E-tosylhydrazone gave 55:45 (n.m.r.).

In work of this type it is important to know whether the relative amount of the two products is determined by kinetic or thermodynamic control. Initially it had been expected that kinetic control would operate and that the two products would not interconvert under the conditions of the reaction, and that there was no selective removal of either isomer after formation by any other path. This was checked experimentally by monitoring the product ratio by h.p.l.c. through the course of a reaction. The ratio remained constant at 55:45 during whole reaction time. This confirms that the product ratio is determined by kinetic control.

To test what effect a more polar solvent would have on the diastereoselectivity, the reaction was repeated in dimethoxyethane. The ratio of the isomers was found to be 56:44 by ^1H n.m.r., a ratio similar to that obtained when cyclohexane was used as the solvent.

The formation of benzodiazepines (67)/(69), Scheme 5, can be rationalised in terms of a 1,7-electrocyclisation to give the non-isolatable intermediates (66) and (68) respectively, thus creating in each case, a new chiral centre at C-4. These subsequently isomerized by a rapid [1,5] sigmatropic hydrogen shift, transferring the chirality without racemization to give the isolated products (67) and (69).



Scheme 5

For the major product to have the configuration of (67), the approach of the diazo-group must have been from the less hindered face of the alkene in its lowest energy conformation as shown in (65), that is, the smallest group (H) in or near the plane of the double bond. As discussed later in Section 2, this conformation of R^C is not necessarily the one adopted in the transition state for cyclisation.

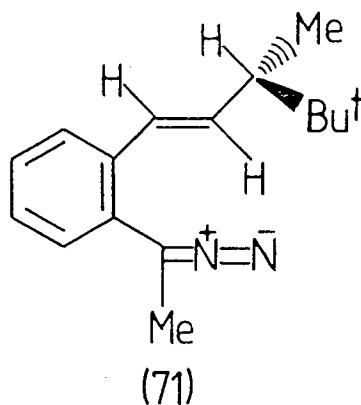
Although the difference is small (10 % d.e.), the result is evidence that a chiral group adjacent to the site of ring closure, does induce asymmetry in the 1,7-electrocyclisation reaction.

1.2. $R^C = 1,2,2$ -Trimethylpropyl.

Following the initial success in detecting asymmetric induction in the 1,7-electrocyclisation, the next aim was to attempt to increase the selectivity.

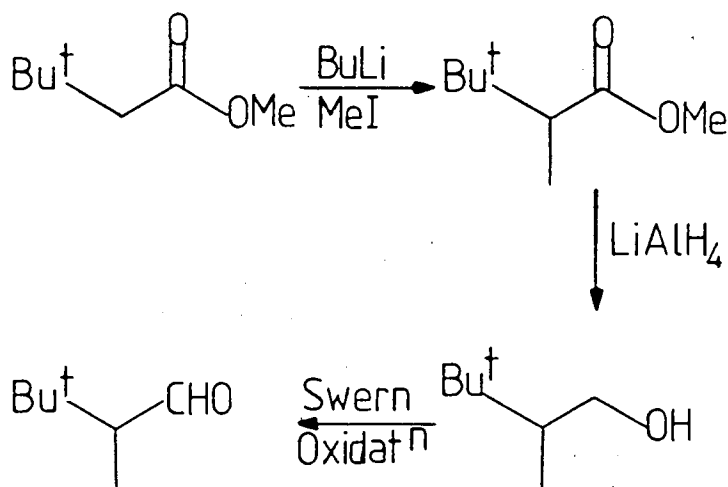
Cherest, Felkin and Prudent¹⁰¹ reported that in the reduction of alpha-chiral open chain aldehydes with lithium aluminium hydride, the greater the size of the large group in the chiral centre, the more stereoselective the reaction became. The tert-butyl group giving the highest stereoselectivity.

Applying the same rationale to our system, that is, by substituting the sterically larger tert-butyl group for the phenyl group, a greater steric interaction should occur between the 1,3-dipole and the tert-butyl group. It was hoped that this would result in an increase in the selectivity of the reaction. Therefore, diazoalkane (71) was the next target molecule.



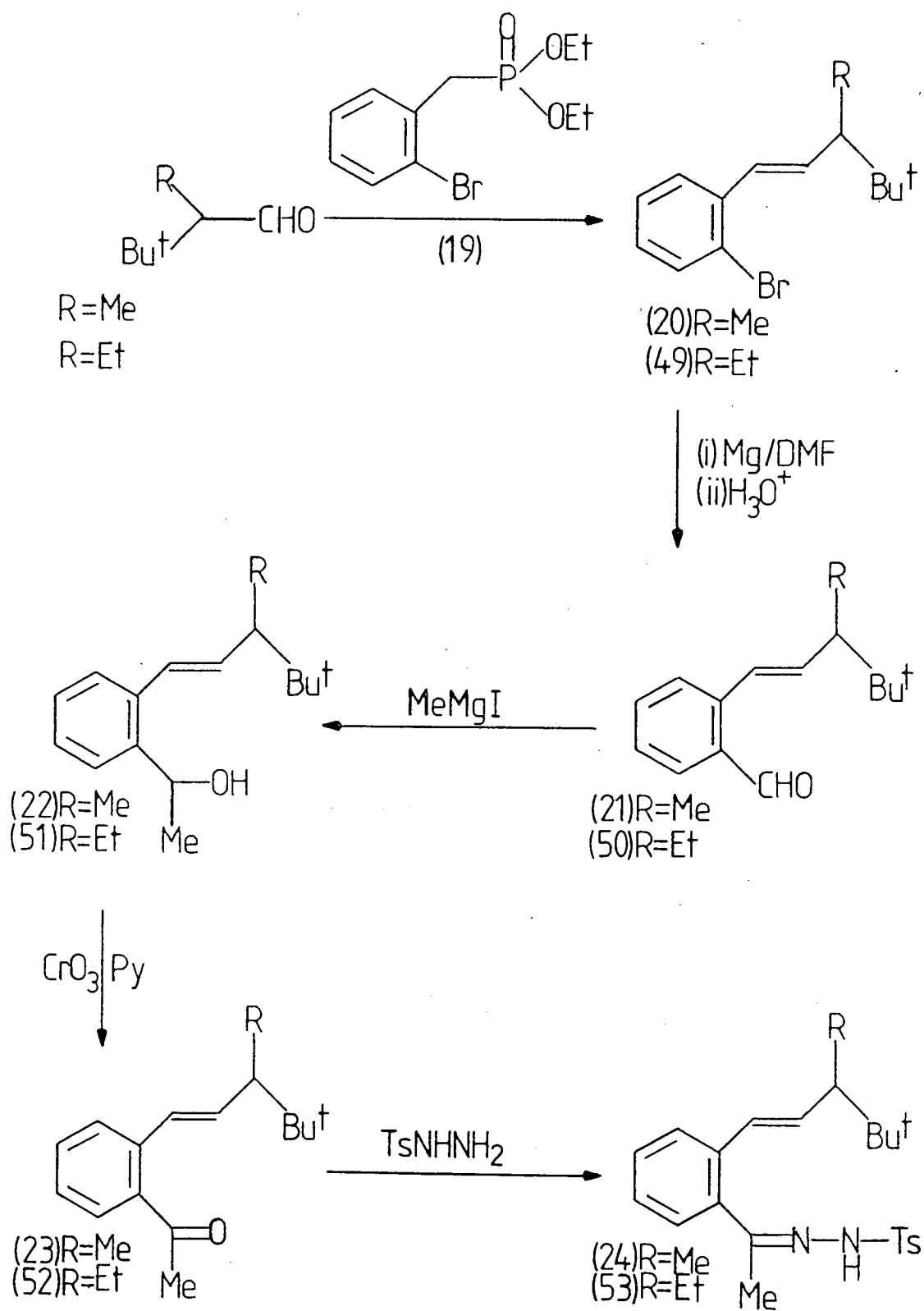
1.2.1. Synthesis of the Chiral Tosylhydrazone Precursors.

The required chiral aldehyde, 2,3,3-trimethylbutanal was prepared by the method of Meyers and Walkup¹⁵⁴ from methyl 3,3-dimethylbutanoate in good yield (Scheme 6).



Scheme 6

In this case, it was decided to avoid the earlier problems with the separation of the E- and Z-bromophenyl alkenes (1)/(2) using the Wadsworth-Emmons reaction¹⁵⁵ instead of the Wittig



Scheme 7

reaction. The Wadsworth-Emmons reaction has been reported¹⁵⁶ to give specifically the E-isomers.

The required phosphonate (19), Scheme 7, was synthesized by an Arbusov reaction¹⁵⁷ between 2-bromobenzyl bromide and triethylphosphite in high yield.

A Wadsworth-Emmons reaction of 2,3,3-trimethylbutanal with the ylide, generated from (19) and lithium diisopropylamide, gave the E-alkene (20) in high yield. A Grignard reagent prepared from (20) and reacted with dimethylformamide, followed by hydrolysis, gave the aldehyde (21). The ketone (23) was prepared by the reaction of the Grignard reagent with the aldehyde (21) to give the alcohol (22); a Jones oxidation gave the ketone (23) in high yield.

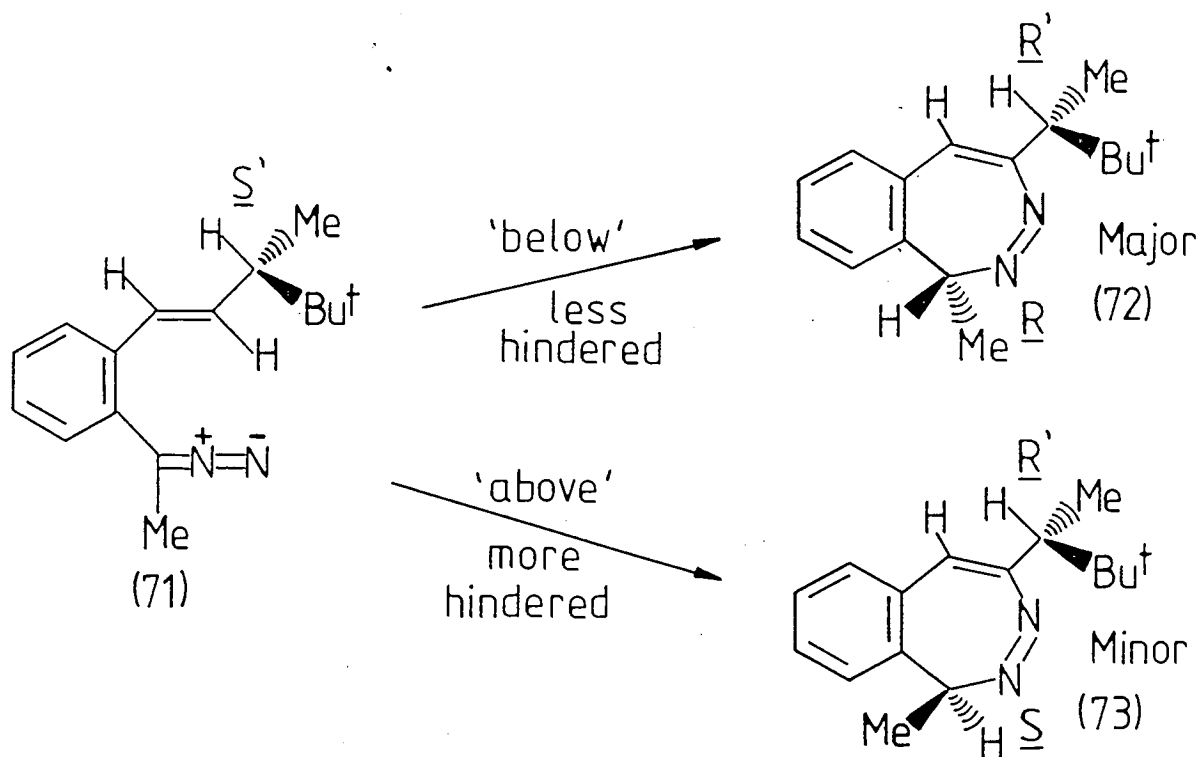
The ketone (23) was converted by a condensation reaction with tosylhydrazide, into the tosylhydrazone (24) under mild conditions. The yield from the synthesis of the bromophenyl alkene (20) to the tosylhydrazone (24) was 67%.

1.2.2. Decomposition of the Tosylhydrazone Sodium Salt.

The diazoalkane (71) was generated as described in 1.1.2., by the Bamford-Stevens reaction of the sodium salt of the tosylhydrazone (24) in cyclohexane. The reaction gave two products, which after chromatography were identified as being 1H-2,3-benzodiazepines by spectral analysis.

The mass spectra of each isomer confirmed that the structure had the formula $C_{16}H_{22}N_2$ and showed a major fragmentation via the loss of a molecule of nitrogen. The 1H n.m.r. and the ^{13}C n.m.r. spectra gave signals, characteristic of 1H-2,3-benzodiazepines.

A crystallographic structure determination carried out on the major isomer, confirmed the benzodiazepine structure and determined the relative stereochemical configuration of the two chiral centres, see Appendix III, Picture 2 and as shown in structure (72) in Scheme 8.



Scheme 8

By deduction, the relative stereochemical configuration of the two chiral centres in the minor isomer, must be that of structure (73).

The ratio of the benzodiazepine diastereomers (72):(73) was measured by ^1H n.m.r. using the integrals of the C-5 hydrogens and confirmed by h.p.l.c. (see Appendix II Diagram 2). The cyclisation gave a ratio of 58:42 by both methods.

To test that the two products do not interconvert during the reaction, and that there was no selective removal of either

isomer, the product ratio was again monitored during the course of a reaction by h.p.l.c.. It was found as expected that the ratio remained constant at 58:42, confirming that the reaction is kinetically controlled.

To test what effect solvent polarity has on the stereoselectivity, the reaction was carried out in dimethoxyethane and dimethylformamide. In these more polar solvents, the ratio was found to be similar to the ratio found in the reaction carried out in cyclohexane. These results suggest that the asymmetric induction found in these reactions, is unlikely to be caused by electronic factors such as polar repulsions or attractions.

The conclusion from the cyclisation of diazoalkane (71), is that to obtain the major isomer configuration (72), the preferred approach of the diazo group must have been from the less hindered face of the alkene in its ground state conformation, as in the previous case ($R^C = \text{Ph, Me, H}$).

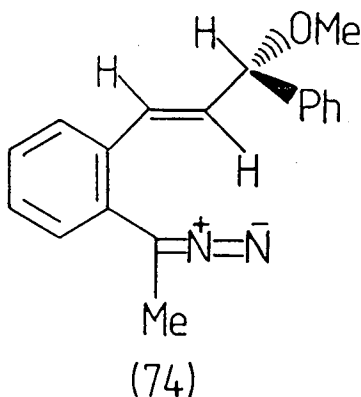
The 16 % d.e. is double that found in the formation of (67)/(69) in Scheme 5. Therefore, it appears that increasing the size of the large group in R^C does indeed improve the diastereoselectivity.

1.3. $R^C = 1\text{-Methoxy-1-phenylmethyl}$.

A literature search uncovered work by Kozikowski and Ghosh¹⁰⁹ on the intermolecular nitrile oxide cycloaddition to chiral allylic ethers (see page 63 of this thesis). They reported diastereoselectivities of > 50 % d.e., much greater than modest results. Therefore, it was thought that these

chiral allylic ethers would be suitable to test in our electrocyclisation reactions.

The proposed diazoalkane (74) was chosen as the next target.



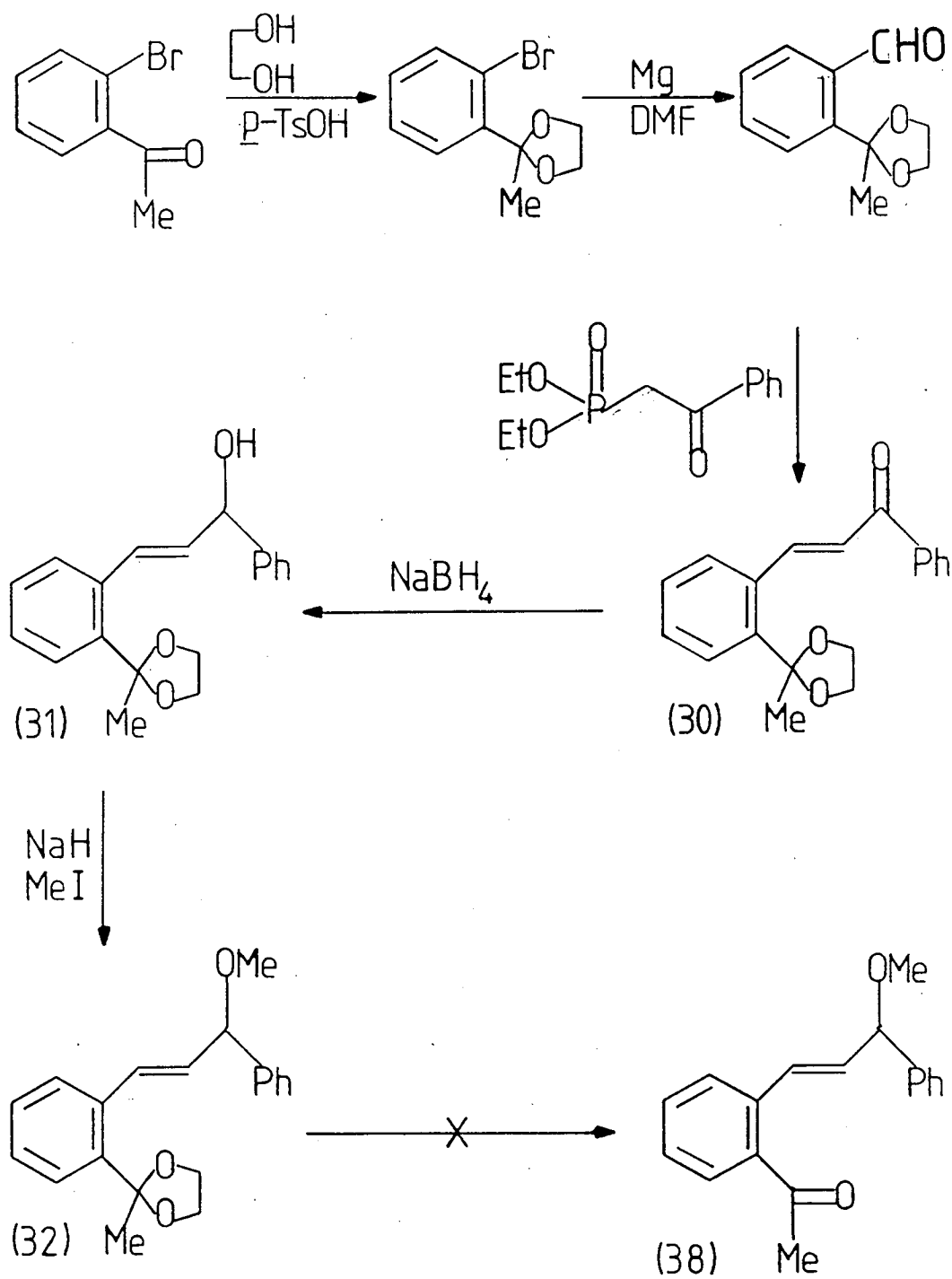
The phenyl group was retained as the large sized group, and for the medium sized group, OMe was chosen because of the its ease of synthesis.

1.3.1. Synthesis of the Chiral Tosylhydrazone Precursors.

The synthesis shown in Scheme 9, was the first route chosen to make the ketone (38).

2-(2'-Bromophenyl)-2-methyl-1,3-dioxolane was prepared by the method of Schiemenz and Kaack¹⁵⁸. Reaction of its Grignard reagent with dimethylformamide gave

2-(2'-methyl-1',3'-dioxalan-2'-yl)benzaldehyde. A Wadsworth-Emmons reaction of the aldehyde with an ylide, generated from diethyl phenacylphosphonate and sodium hydride gave the E-enone (30) in high yield. Sodium borohydride reduction at -20°C, gave the alcohol (31), quantitatively. Methylation of the alcohol was achieved by a procedure described by



Scheme 9

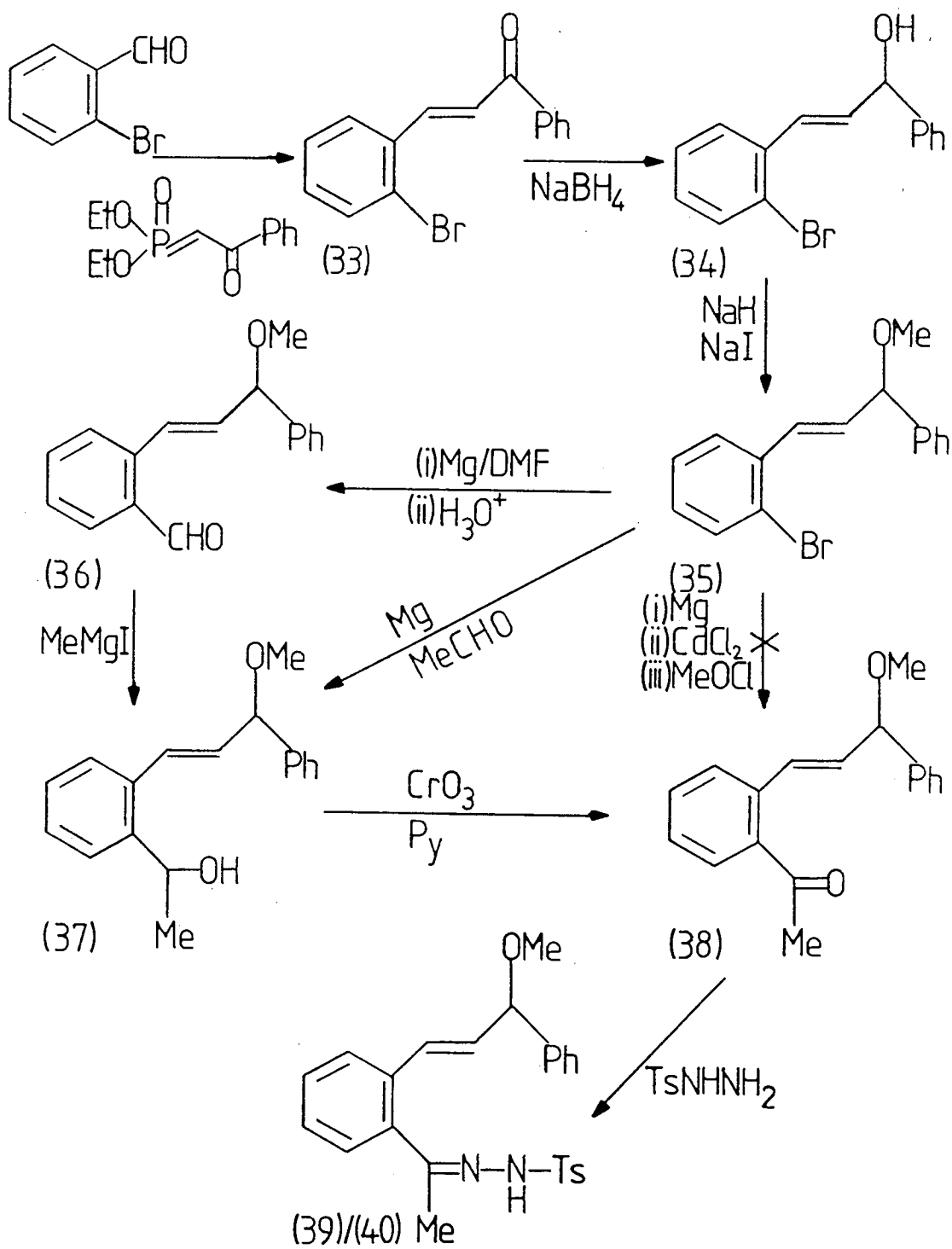
Stoochnoff and Benoiton¹⁵⁹ using sodium hydride and methyl iodide.

However, attempts to deprotect (32) to give the ketone (38) were unsuccessful. For example, stirring (32) in methylene chloride with 10 % w/w aqueous oxalic acid adsorbed onto silica gel¹⁶⁰ gave only a multi-component mixture, none of which were the ketone (38). Substitution of 15 % v/v aqueous sulphuric acid for the oxalic acid solution, also failed to give the required product. Other methods were attempted; hydrochloric acid in ethanol¹⁶¹, pyridinium *p*-toluenesulphonate¹⁶², and glacial acetic acid¹⁶³. All of which gave multi-component mixtures. The i.r. spectra of the crude oil from each attempt showed that the expected carbonyl peak was absent.

The conclusion from this work was that the stronger forcing conditions required to deprotect the ketal, in comparison to acetals, were detrimental to the allylic ether group. This was further confirmed by the absence of the methoxy group in the crude reaction mixtures examined by ¹H n.m.r..

An alternative synthesis was proposed, substituting 2-bromobenzaldehyde for 2-(2'-methyl-1',3'-dioxalan-2'-yl) benzaldehyde as shown in Scheme 10. The original aim was to generate the ketone (38) from the bromophenyl derivative (35) in a single stage synthesis.

A Wadsworth-Emmons ^{reaction} between 2-bromobenzaldehyde and the same ylide as before, gave (33) in good yield. Sodium borohydride reduction at a lower temperature of -30°C, gave the alcohol (34), quantitatively. The allylic ether (35) was



Scheme 10

obtained^{by} methylation of the alcohol (34). A one step synthesis of (38) by a procedure¹⁶⁴ employing an organocadmium reagent of (35) was attempted. However, the ¹H n.m.r. spectra of the resulting crude mixture showed that none of the ketone (38) had been formed. An alternative approach was attempted¹⁶⁵, using a Grignard reagent formed from (35) and adding to it N,N-dimethylacetamide. After hydrolysis, the major component was found to be the hydrocarbon resulting from the hydrolysis of the Grignard reagent.

As an alternative to the direct route to the ketone, acetaldehyde was added to the Grignard reagent of (35). This gave the expected alcohol (37), but in poor yield. Finally, to solve this synthesis problem, the synthetic route described in both the earlier sections was used.

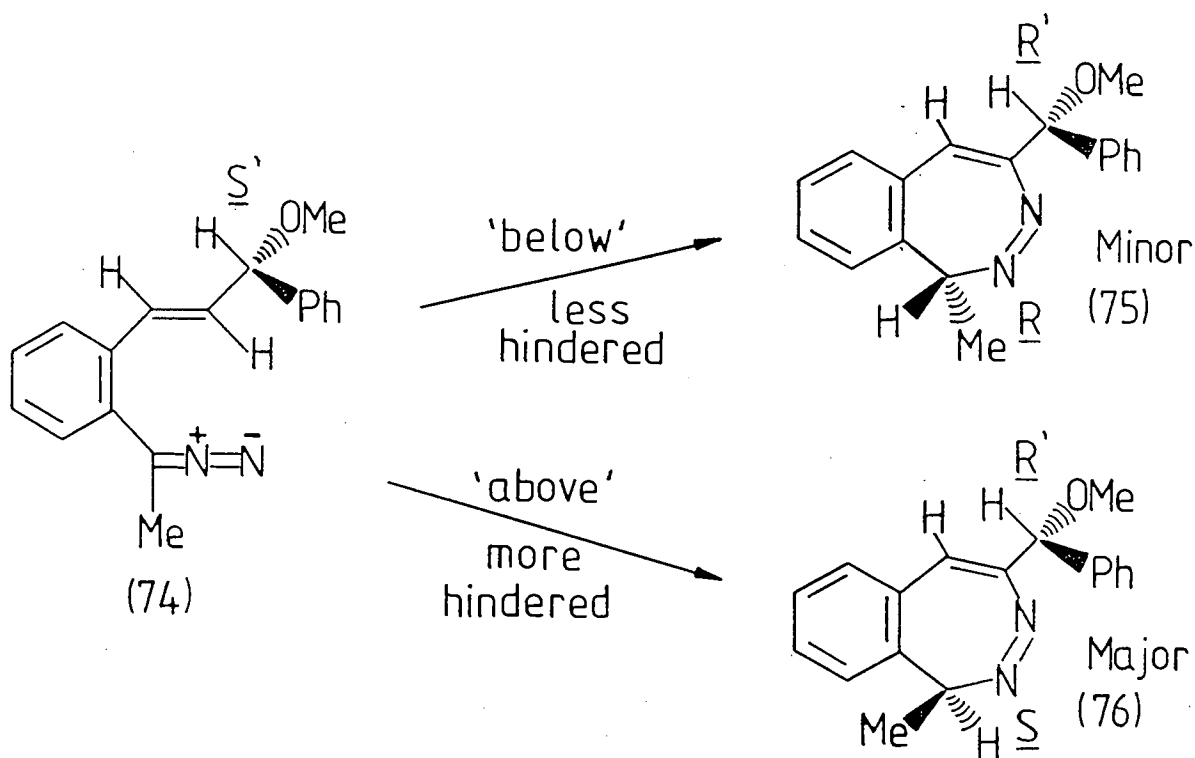
Aldehyde (36) was generated by reaction of the Grignard reagent of (35) with dimethylformamide. The ketone (38) was finally prepared by the addition of a methyl magnesium iodide reagent to (36) to give the alcohol (37); followed by a Jones oxidation.

A condensation reaction between (38) and tosylhydrazide gave the syn- and anti-tosylhydrazones (39) and (40), respectively. The yield from (33) to the tosylhydrazones (39)/(40) was 22%.

1.3.2. Decomposition of the Tosylhydrazone Sodium Salt.

The diazoalkane (74) was generated in cyclohexane in the usual manner. After 5h, the tosylhydrazone was consumed, to give the expected products. Each diastereomer was separated by chromatography and characterized by spectral analysis.

A crystallographic structure determination carried out on the major isomer, confirmed the benzodiazepine structure and determined the relative stereochemical configuration of the two chiral centres. The result is shown in structure (76) in Scheme 11 (see Appendix III, Picture 3).



Scheme 11

Therefore, the relative stereochemical configuration of the two chiral centres in the minor isomer, must be that of structure (75).

The ratio of the benzodiazepine diastereomers (75):(76) was measured by ^1H n.m.r. using the integrals of the C-5 hydrogens and confirmed by h.p.l.c. (see Appendix II, Diagram 3). The cyclisation gave a ratio of 44:56 by both methods.

The product ratio was again monitored during the course of a reaction by h.p.l.c.. It was found as expected that the

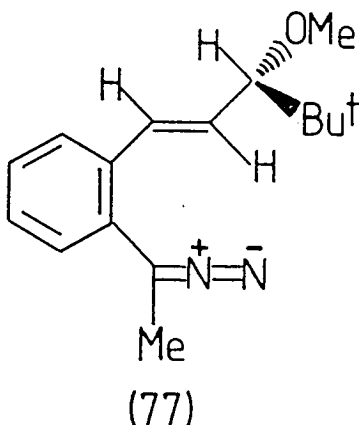
ratio remained constant at 44:56, confirming again, that the reaction is kinetically controlled.

The conclusion from the cyclisation of diazoalkane (74), is that to obtain the major isomer configuration (76), the preferred approach of the diazo-group must have been from the more hindered face of the alkene in its ground state conformation, as shown in (74). A striking difference was noted, in that the preference for the more hindered face is the opposite to that observed in the earlier cyclisations of diazoalkanes (65) and (71). This suggests that the presence of an oxygen atom within the chiral group has radically changed the previously observed asymmetric induction. However, the selectivity was lower than hoped for (12 % d.e.), and it was decided to find out if the selectivity could be improved by substituting a larger substituent for the phenyl group.

1.4. R^C = 1-Methoxy-2,2-dimethylpropyl.

The diastereoselectivity of the cyclisation of diazoalkane (74) was small. It was hoped that a substitution of the phenyl group by the sterically larger tert-butyl group would improve the selectivity caused by the chiral alkoxy ethers.

The next target molecule was diazoalkane (77).



If the more hindered face preference is found again, then an investigation into the factors causing this reversal of the selectivity would begin.

1.4.1. Synthesis of the Chiral Tosylhydrazone Precursor.

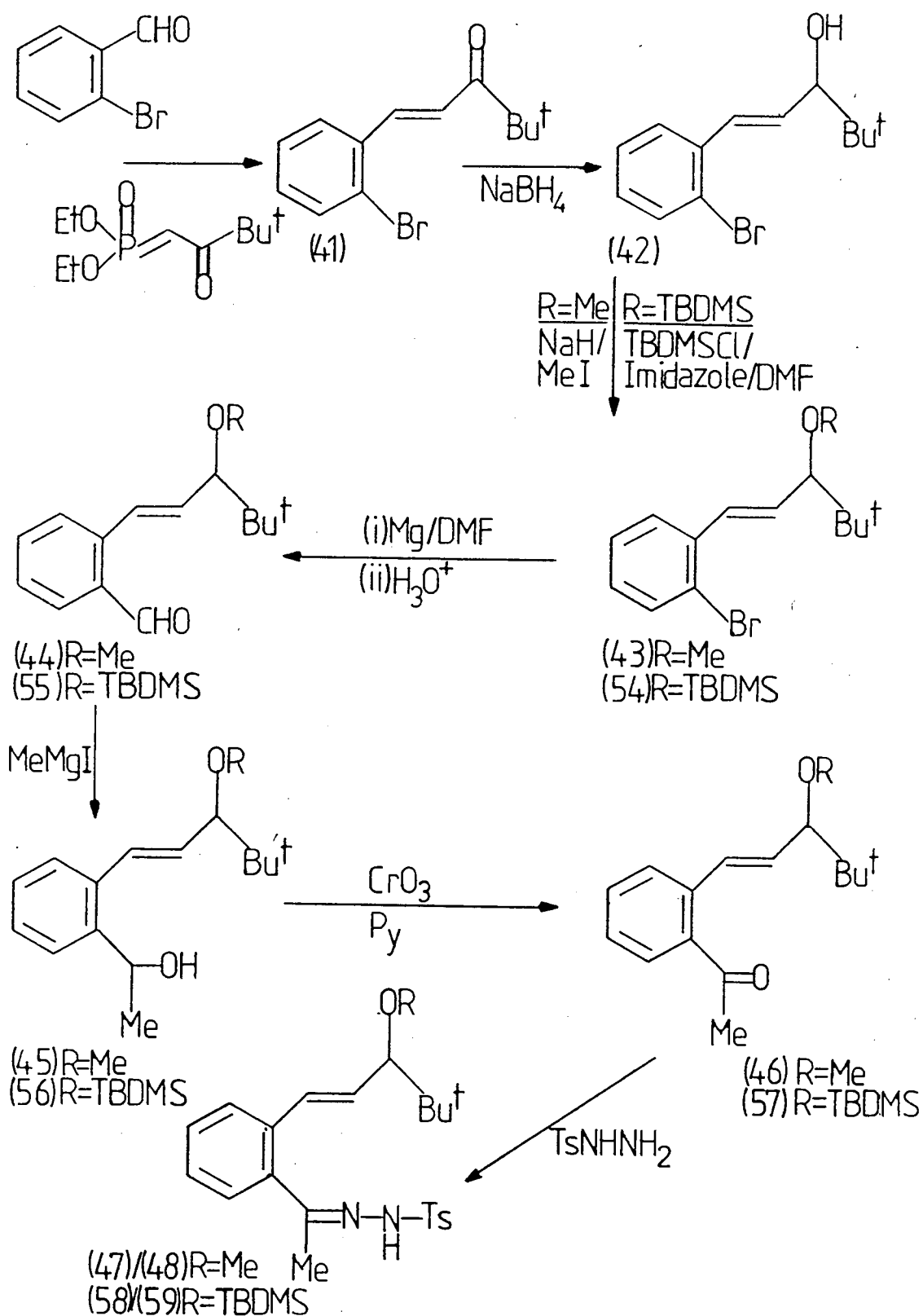
The synthetic route to the tosylhydrazone was proposed, as shown in Scheme 12.

Diethyl (3,3-dimethylbutan-2-one)phosphonate was synthesized by a procedure described by Mathey and Savignac¹⁶⁶. A Wadsworth-Emmons reaction of 2-bromobenzaldehyde with the ylide, generated from the phosphonate and sodium hydride gave the E-ketenone (41) in high yield. Reduction of (41) using sodium borohydride at -25°C gave the alcohol (42), quantitatively; methylation of the alcohol (42) give the ether (43), in high yield. Aldehyde (44) was generated by reaction with the Grignard reagent of (43) with dimethylformamide, followed by hydrolysis. The ketone (46) was prepared by the addition of a methyl magnesium iodide reagent to (44) to give the alcohol (45); followed by a Jones oxidation.

A condensation reaction between (46) and tosylhydrazide gave the syn- and anti-tosylhydrazones (47) and (48), respectively. The yield from (41) to the tosylhydrazones (47)/(48) was 36%.

1.4.2. Decomposition of the Tosylhydrazone Sodium Salts.

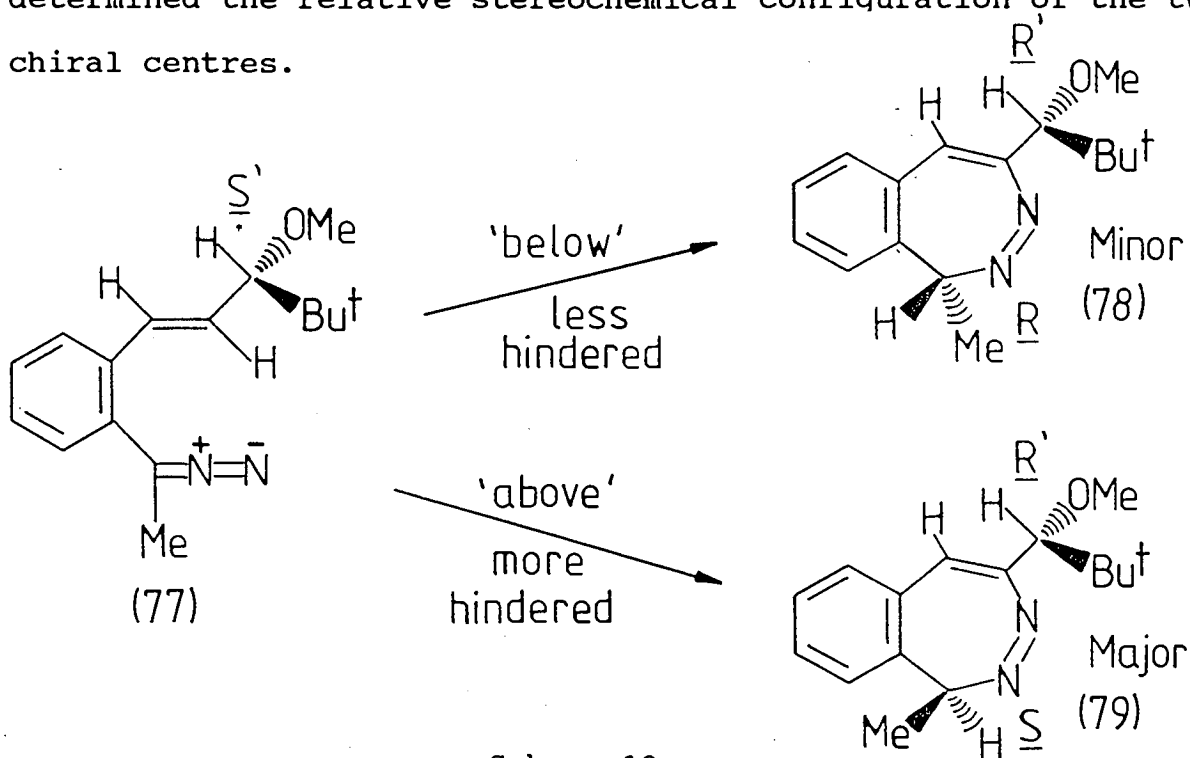
The diazoalkane (77) was generated in cyclohexane as previously described. After 1.5h, the tosylhydrazone salt was all consumed, giving the expected products. Each diastereomer



Scheme 12

was then separated by chromatography and characterized by spectral analysis as being the expected benzodiazepines.

A crystallographic structure determination carried out on the major isomer, confirmed the benzodiazepine structure and determined the relative stereochemical configuration of the two chiral centres.



Scheme 13

The result is shown in structure (79) in Scheme 13 (see Appendix III, Picture 4). The relative stereochemical configuration of the minor isomer is shown in structure (78).

The ratio of the benzodiazepine diastereomers (78)/(79) was found to be 8:92 by ^1H n.m.r. and 10:90 by h.p.l.c. (see Appendix II, Diagram 4). As found with the group $\text{R}^{\text{C}}=\text{Ph}, \text{OMe}, \text{H}$ the preferred approach of the diazo-group must have been from the more hindered face of the alkene in its lowest energy conformation (77).

A diastereoselectivity of 84 % d.e. was the highest obtained so far. It is evident that changing to the larger steric bulk of the tert-butyl group has had a major effect of increasing the

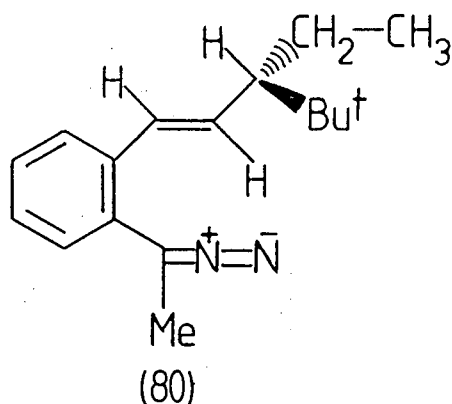
selectivity. A detailed explanation of these differences in selectivity is presented in the Section 2. Briefly, the high selectivity may result from a combination of steric and electronic factors. To test for the influence of electronic polar effects, the reaction was repeated in dimethoxyethane and dimethylformamide. The ratio of the products (78):(79) was found to be 10:90 (n.m.r.) and 13:87 (h.p.l.c.) in dimethoxyethane and 16:84 (n.m.r. and h.p.l.c.) in dimethylformamide.

This loss of selectivity with increasing solvent polarity is consistent with the view that polar repulsions or attractions are an important factor in determining the preferred reaction path. It is thought that polar repulsions involving the methoxy oxygen may be important; further discussion is provided in Section 2.

In an attempt to find out whether steric factors were also important in determining the diastereoselectivity found in the cyclisation of (77), it was decided to synthesize a non-polar analogue of (77), with the oxygen replaced by methylene group.

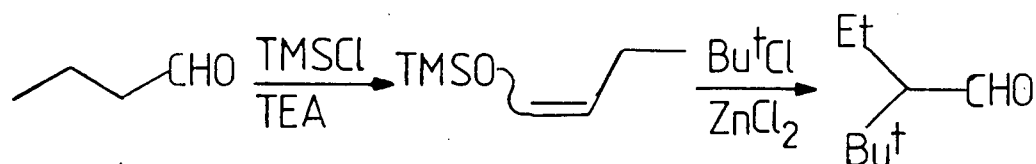
1.5. R^C=1-Ethyl-2,2-dimethylpropyl.

The absence of oxygen in (77) will remove the electronic polar factors. The shape of the chiral group is essentially retained by the methylene's substitution of the oxygen. Therefore, the next target molecule (80) should allow us to test whether steric factors influence the diastereoselectivity in (77).



1.5.1. Synthesis of the Chiral Tosylhydrazone Precursors.

The required chiral aldehyde 2-ethyl-3,3-dimethylbutanal was prepared by the method of Reetz *et al*¹⁶⁷ (Scheme 14).



Scheme 14

A Wadworth-Emmons reaction of the aldehyde with the ylide, generated from the phosphonate (19) and lithium diisopropylamide gave the *E*-alkene (49) in good yield (Scheme 8). The tosylhydrazone (53) was then prepared by the route described in 1.2.1.. The yield from the synthesis of (49) to the tosylhydrazone (53) was 41 %.

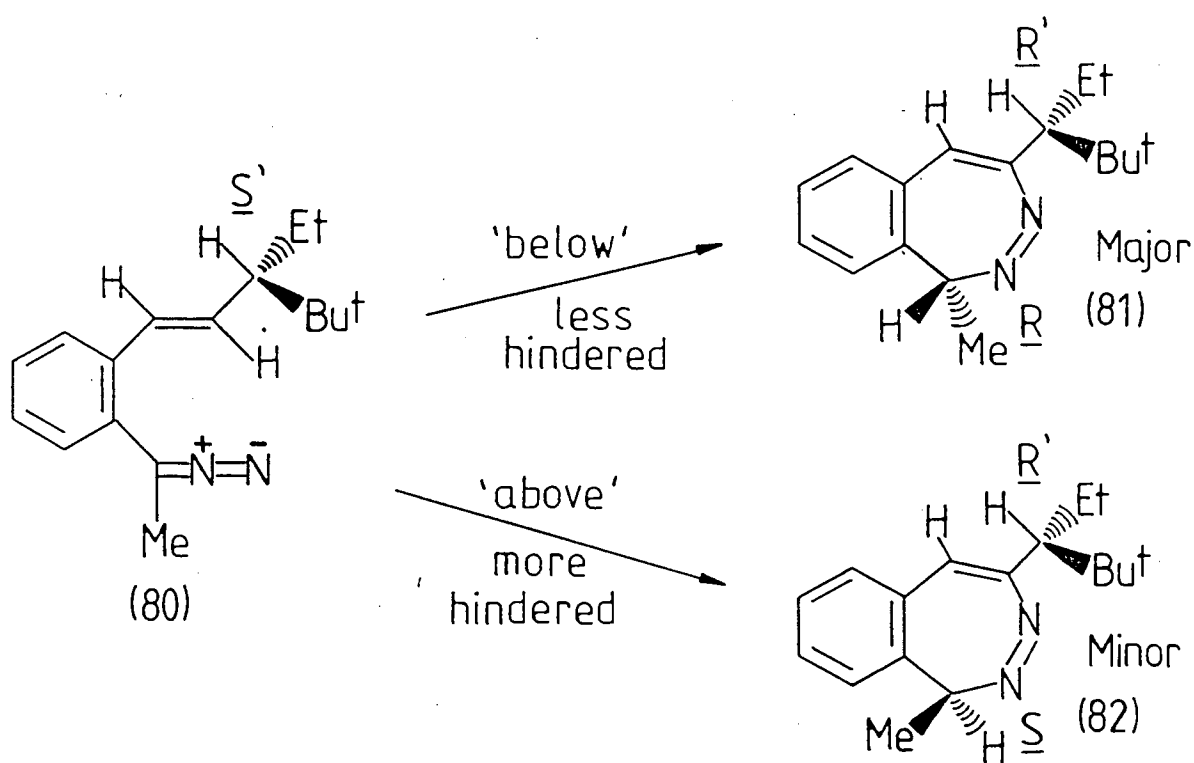
1.5.2. Decomposition of the Tosylhydrazone Sodium Salt.

The diazoalkane (80) was generated in cyclohexane as previously described. After 1.5h, the tosylhydrazone salt was all consumed, giving two yellow products. Each diastereomer

was then separated by chromatography and characterized by spectral analysis as being the expected benzodiazepines.

The major isomer's relative stereochemical configuration was assigned by comparison of the chemical shift values of the C-5 hydrogens in its ^1H n.m.r. spectra, with those of benzodiazepines (72)/(73) (now confirmed by an X-ray structure determination, see Appendix III, Picture 5).

From this comparison, the major isomer's structure was determined to be similar to the major isomer (72) and assigned the structure (81) in Scheme 15. The minor isomer was assigned again by comparison, the configuration (82).



Scheme 15

The ratio of the benzodiazepine diastereomers (81)/(82) was found to be 63:37 by ^1H n.m.r. and 65:35 by h.p.l.c. (see Appendix II, Diagram 5).

For (80) to have cyclised to give the major isomer (81), the diazo-group approached from the less hindered face of the alkene as shown in (80).

This result clearly shows that in the absence of electronic factors, asymmetric induction favours attack on the less hindered face of the alkene by the diazo-group. This facial preference is the opposite to $R^C=Bu^t, OMe, H$. To further test that the asymmetric induction was purely steric in origin, the reaction was repeated in dimethoxyethane and dimethylformamide. The ratio of benzodiazepines remained unchanged in both solvents, confirming that electronic polar effects were not present.

Cyclisation of (80) favouring attack from the less hindered face is the opposite to that obtained by its methoxy analogue (79). This confirms that the asymmetric induction found in the cyclisation of (79) must be largely due to electronic polar factors. Furthermore, the difference in the diastereoselectivity (26 % d.e. when $R^C=Bu^t, Me, H$ and 84 % when $R^C=Bu^t, OMe, H$) reveals that these electronic polar effects are more potent in their effect.

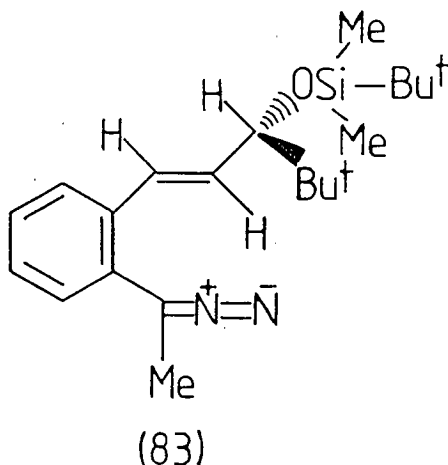
1.6. $R^C=1-(tert\text{-}Butyldimethylsilyloxy)-2,2\text{-}dimethylpropyl$ (OTBDMS).

The highest selectivity observed so far, was that of the methoxy group in (79) (84 % d.e.), apparently caused by electronic polar factors. The general objective of the next stage was to determine what effect changing the polar properties of the oxygen atom would have on the selectivity.

The chiral directing groups (OTBDMS, OH, OCOPh, O⁻) in the following sections were selected for this study.

1.6.1. Synthesis of the Chiral Tosylhydrazone Precursor.

The first example discussed is that of the OTBDMS derivative (83).



The precursor to this diazo-compound was prepared as an intermediate en route to the hydroxy derivative (60). The TBDMS group is a very popular hydroxy protecting group which is surprisingly stable to acids and bases, but is readily removed by the fluoride ion¹⁶⁸. It was felt that it would be of interest to generate (83), as it would provide information on what effect increasing the size of the oxygen substituent would have on the selectivity.

The alcohol (42) in Scheme 12, was reacted with tert-butyldimethylsilyl chloride by a procedure described by Corey¹⁶⁸ to give the silyl ether (54) in quantitative yield. The ketone (57) was then prepared as described in 1.4.1.. Condensation of the ketone (57) with tosylhydrazide gave inseparable syn- and anti-tosylhydrazones (58)/(59). The

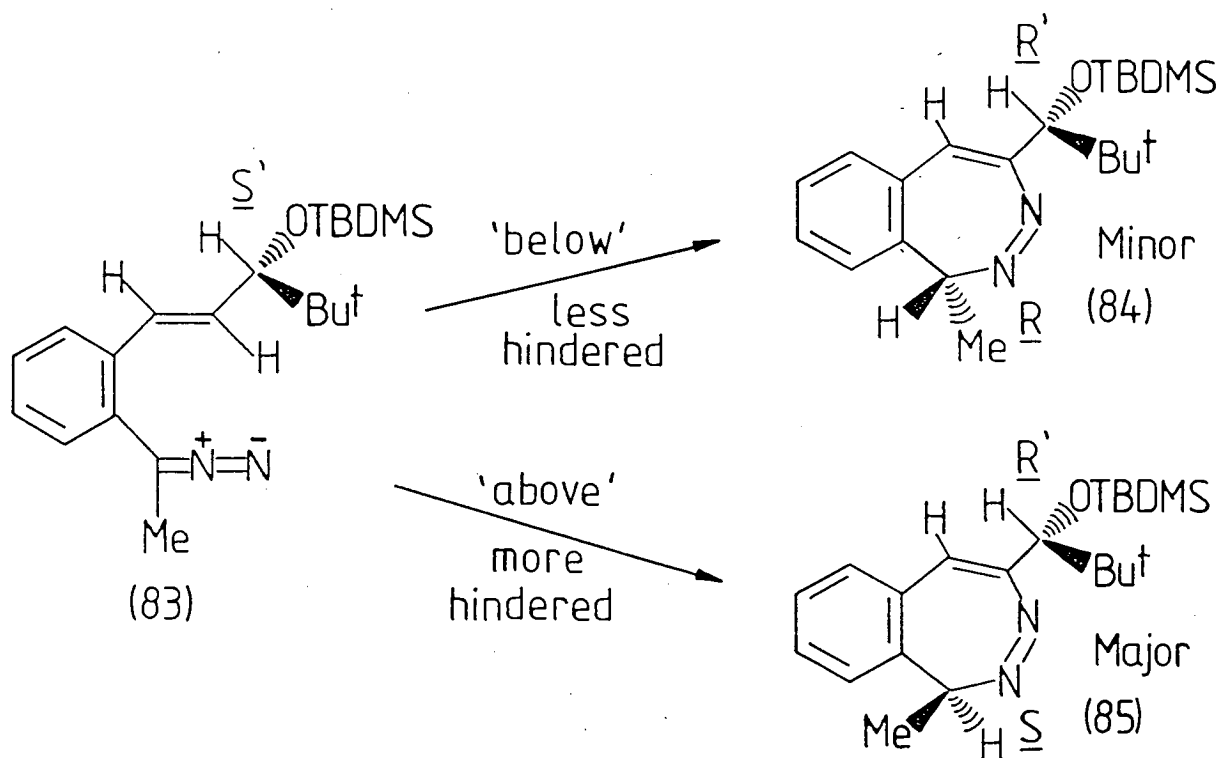
overall yield from enone (41) to the tosylhydrazones (58)/(59) was 51 %.

1.6.2. Decomposition of the Tosylhydrazone Sodium Salts.

The diazoalkane (83) was cyclised in the usual fashion. After 2h, the reaction gave the expected products. Each diastereomer was then separated by chromatography and characterized by spectral analysis as being the expected benzodiazepines.

The major isomer's relative stereochemical configuration was assigned by comparison of the chemical shift values of the C-5 hydrogens in its ^1H n.m.r. spectra, with those of benzodiazepines (78)/(79) ($\text{R}^{\text{C}}=\text{Bu}^{\text{t}}, \text{OMe}, \text{H}$).

From this comparison, the major isomer's structure was determined to be that of structure (85) in Scheme 16. The minor isomer was assigned the configuration (84).



Scheme 16

Therefore, for (83) to have cyclised to give the major isomer (85), the diazo-group approached from the more hindered face of the alkene as shown in (83).

The ratio of the diastereomers (84)/(85) was found to be 9:91 by ^1H n.m.r. and 10:90 by h.p.l.c. (see Appendix II, Diagram 6). As expected, the diazo-group approached from the more hindered face of the alkene. But, what is surprising, is that the diastereoselectivity (82% d.e.) is very similar to that obtained when $\text{R}^{\text{C}}=\text{Bu}^{\text{t}}, \text{OMe}, \text{H}$. The conclusion from this result is that the oxygen substituent does not have much steric influence over the asymmetric induction.

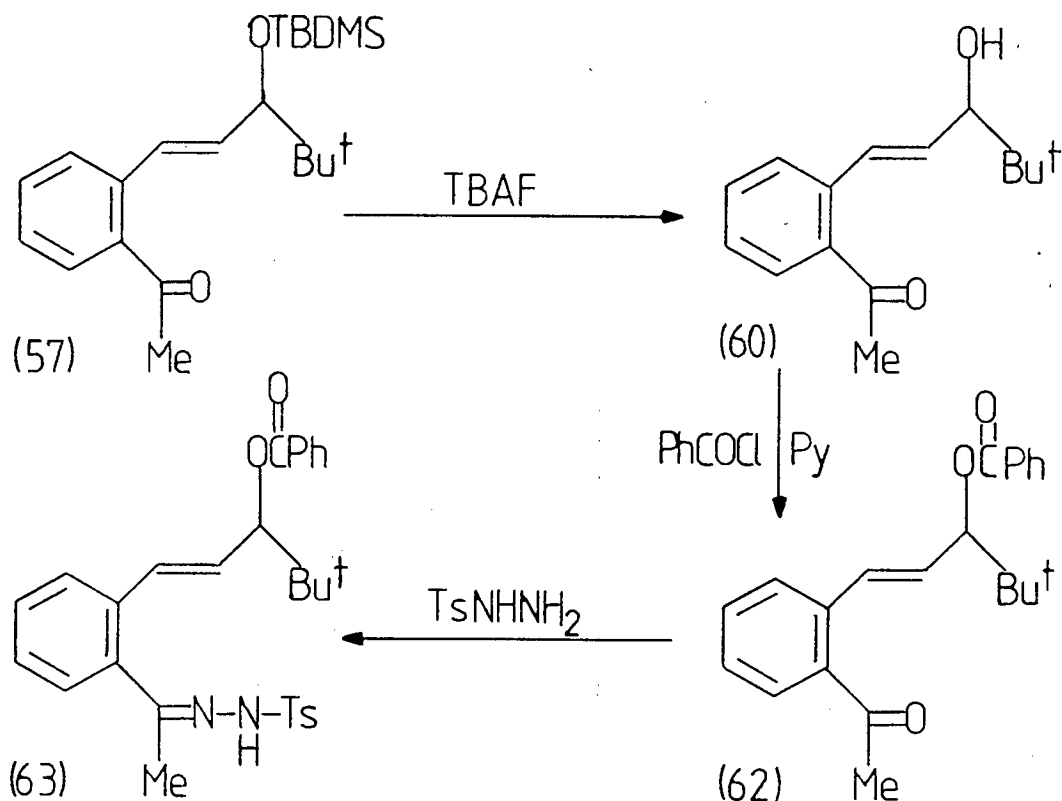
Further reactions were carried out in the solvents dimethoxyethane and dimethylformamide. The product was found to be 11:89 by ^1H n.m.r. in dimethoxyethane and 12:88 by ^1H n.m.r. in dimethylformamide. The loss of diastereoselectivity is not as great as the loss when $\text{R}^{\text{C}}=\text{Bu}^{\text{t}}, \text{OMe}, \text{H}$. This suggests that the large bulk of the TBDMS group reduces the electronic polar factors' susceptibility to high polarity.

1.7. $\text{R}^{\text{C}}=2,2\text{-Dimethylpropyl-1-benzoate}$.

The intention here was to change the polar properties of the oxygen by the attachment of the electron withdrawing benzoyl group. Furthermore, it was planned to vary this effect by using electron withdrawing or donating substituents in the aromatic ring.

1.7.1. Synthesis of the Chiral Tosylhydrazone Precursor.

The deprotection of ketone (57) was achieved using T.B.A.F.¹⁶⁸ (Scheme 17).



Scheme 17

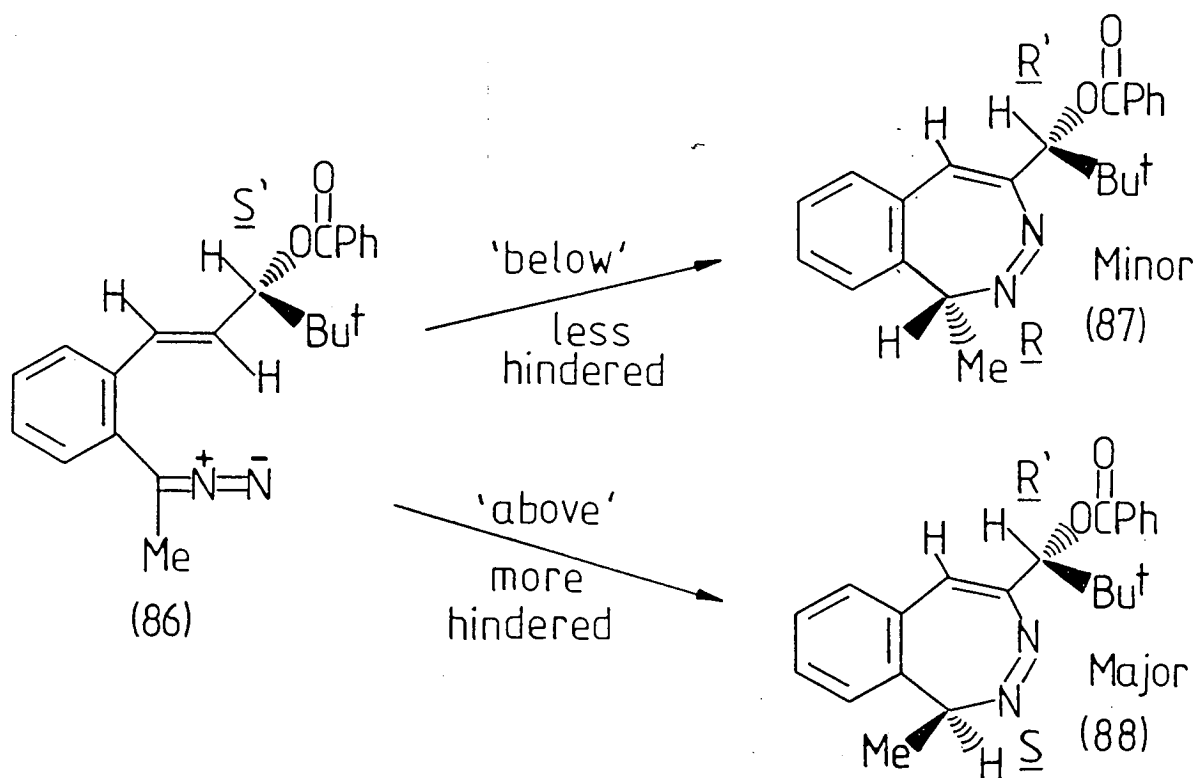
The resulting keto-alcohol (60) was added to benzoyl chloride in pyridine to give the benzoate ester (62). Condensation of (62) with tosylhydrazide gave the syn- and anti-tosylhydrazones (63) and (64). The yield from (57) to the tosylhydrazones (63)/(64) was 74%.

1.7.2. Decomposition of the Tosylhydrazone Sodium Salts.

The diazoalkane (86) was cyclised in the usual fashion. After 1h, the reaction gave the expected products. Each diastereomer was then separated by chromatography and characterized by spectral analysis as being the expected benzodiazepines.

A crystallographic structure determination carried out on the minor isomer (better crystals), confirmed the benzodiazepine structure and determined the relative stereochemical configuration of the two chiral centres (see

Appendix III, Picture 6). The relative configuration of the minor isomer is shown in structure (87) in Scheme 18. Therefore, the major isomer was assigned the structure (88).



Scheme 18

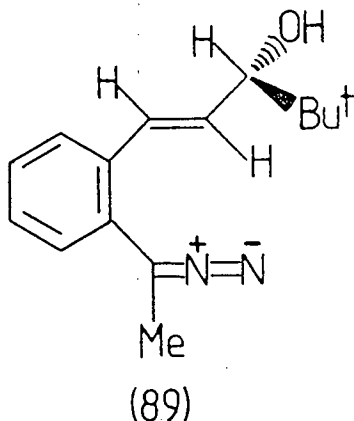
The ratio of the diastereomers (87)/(88) was found to be 41:59 by ¹H n.m.r. (see Appendix II, Diagram 8).

Therefore, for (86) to have cyclised to form the major isomer (88), the diazo-group approached from the more hindered face of the alkene in its ground state conformation.

The loss of diastereoselectivity (18% d.e.) must be attributed to the electron withdrawing effect of the benzoate ester. It is unlikely that steric factors participate, as the earlier case R^C=Bu^t, OTBDMS, H had shown that the size of the oxygen substituent does not effect the diastereoselectivity. This result is discussed further in Section 2.

1.8. R^C=1-Hydroxy-2,2-dimethylpropyl.

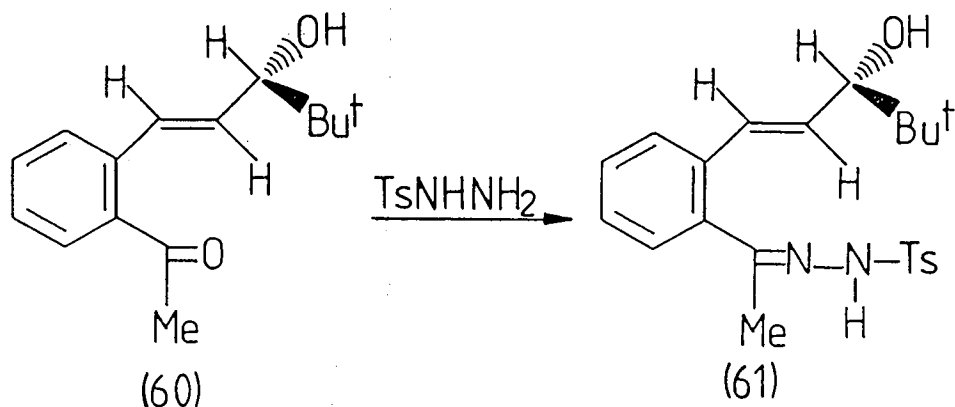
As a continuation of the study into the effect of varying the nature of the polar properties of the oxygen atom, the diazoalkane (89) was chosen as the next target.



Given the relatively high acidity of the N-H hydrogen in the tosylhydrazone (61) in Scheme 15, it was expected that it would be preferentially abstracted by base. It was hoped therefore that the diazoalkane could be generated via the careful addition of one equivalent of butyllithium at a low temperature to a solution of the tosylhydrazone (61), to give the tosylhydrazone salt with the hydroxy group still intact.

1.8.1. Synthesis of the chiral tosylhydrazone precursor.

The required tosylhydrazone (61) was prepared by condensation of the alcohol (60) with tosylhydrazide under mild conditions (Scheme 19).



Scheme 19

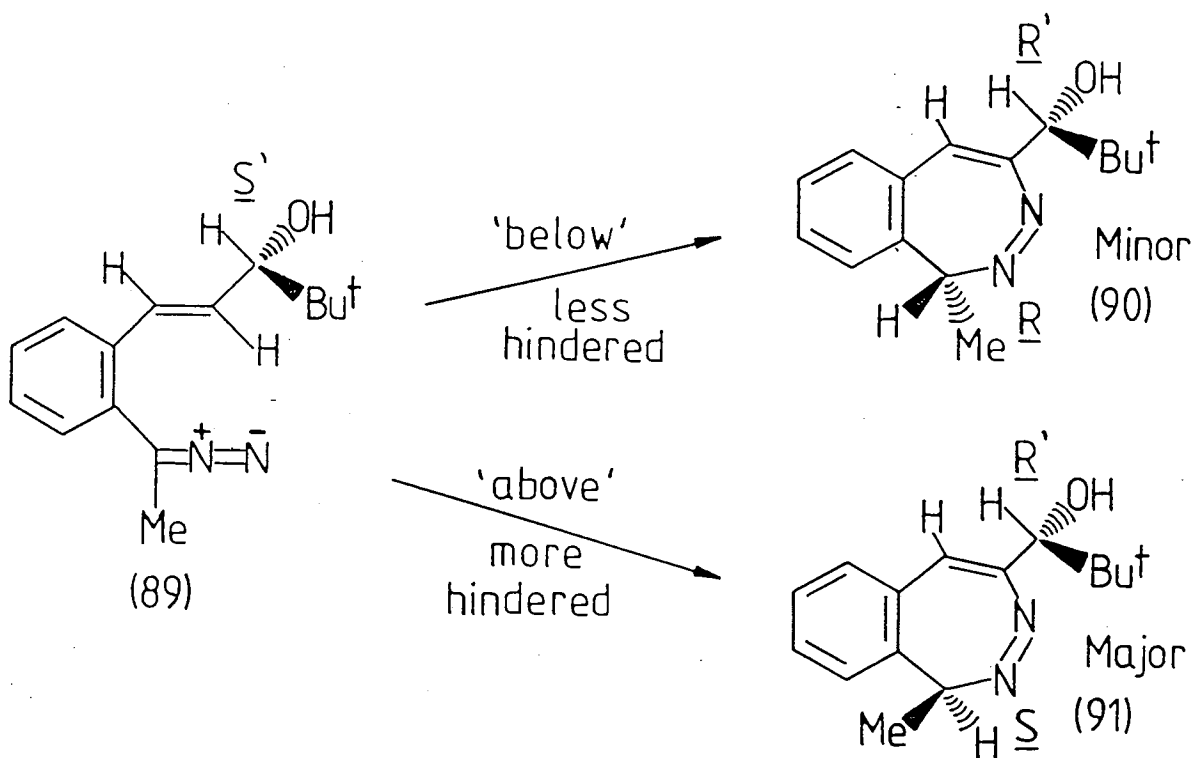
1.8.2. Decomposition of the lithium salt of the tosylhydrazone.

The lithium salt was prepared by the addition of a one mole equivalent of butyllithium to a solution of the tosylhydrazone (61) in dimethoxyethane at -40°C . An earlier attempt to carry out the electrocyclisation in cyclohexane failed, because of the insolubility of the tosylhydrazone lithium salt.

The mixture was allowed to reach ambient temperature, and then slowly heated to reflux to generate the diazoalkane (89). The formation of the products was monitored by h.p.l.c.. After 2.25h, all of the tosylhydrazone salt was consumed, giving two products only.

Separation of the diastereomers could not be accomplished by chromatography. However, spectral analysis identified

the products as being the expected benzodiazepines (90) and (91) (Scheme 20). Further identification was obtained by a comparison of the ^1H n.m.r. spectra of the mixture with a spectrum of a sample of the isomer (91) prepared by fluorodesilylation of benzodiazepine (85) ($\text{R}^{\text{C}}=\text{Bu}^{\text{t}}$, OTBDMS, H). It was found that the ^1H n.m.r. spectrum of (91) was identical with the spectrum of the major isomer found in the mixture. As it was known that (85) was formed by the diazo-group approaching, from the more hindered face of the alkene in its ground state conformation; benzodiazepine (91) must have been formed in the same manner. The minor isomer was assigned the configuration (90).



Scheme 20

The ratio of diastereomers (90)/(91) on the crude material was found to be 29:71 by ^1H n.m.r. and 28:72 by h.p.l.c. (see Appendix II, Diagram 9).

It is notable that although the d.e. is lower (42% d.e.) than for (78)/(79) ($R^C = \text{Bu}^t, \text{OMe}, \text{H}$), the preference is still in the same direction.

1.9. $R^C = 2,2$ -Dimethylpropyl-1-oxide ion.

One of the main reasons for embarking on this series of experiments was to examine the effect of having $M = \text{O}^-$. As a tentative explanation of the high diastereoselectivity obtained when $M = \text{OR}$, it had been postulated the polar repulsion between the alkoxy oxygen and the diazogroup's leading nitrogen was key factor in determining the preferred reaction path. It was thought therefore, that this effect might be enhanced and thus the selectivity increased by placing a full negative charge on the oxygen.

1.9.1. Synthesis of the Chiral Tosylhydrazone Precursor.

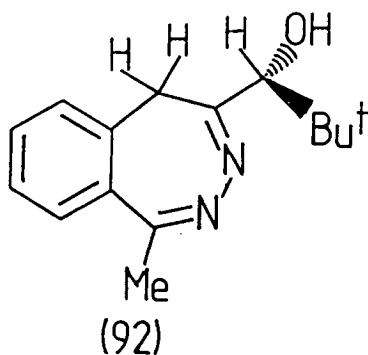
An excess of butyllithium (2.2 molar equivalents) was added to a cold solution of the tosylhydrazone (61) in dimethoxyethane.

1.9.2. Decomposition of the Tosylhydrazone Sodium Salts.

The solution from 1.9.1 was heated slowly to reflux. After 4h, all the tosylhydrazone was consumed, giving the expected benzodiazepines (90)/(91). The diastereomer ratio was found to be 97:3. The pure major isomer (90) was obtained by recrystallisation and a portion silylated to compare its structure with that of the known silylated benzodiazepine (84). The ^1H n.m.r. spectra were identical (see Appendix,

Diagram 7), confirming that the formation of (90) was by the diazo-group approaching from the less hindered face of the alkene in its ground state conformation; the opposite of what occurs for M= methoxy, hydroxy, and OTBDMS.

This result was so remarkable that the reaction was examined very carefully to find out whether some new factor was involved, such as epimerisation at C-1 in the benzodiazepine by the excess base to give what was perhaps the more stable product. The reaction was therefore repeated with careful monitoring by h.p.l.c.. It was observed that the ratio of the isomers (90)/(91) changed with time (for details see p245 of this thesis). In addition, a third compound formed in the reaction was detected by h.p.l.c.; its proportion was found to increase with time. This component was later isolated by chromatography and identified as being the 5H-benzodiazepine (92).



This formation of 5H-isomers by the base isomerisation of the 1H-benzodiazepines has been established by earlier workers⁷⁶. To confirm that the excess base was converting the isomers (90)/(91) to the 5H-isomer (92), the reaction was repeated, but with a portion of pure (91) added to enrich the

mixture with the minor product. However, after 5h the product ratio (90):(91) was found to be 100:0 [a 38% yield of (90) and a 21% yield of (92)]. This result clearly shows that (91) is the least stable of the isomers under the reaction conditions.

It was postulated that two pathways to rearrangement were possible. Either, proton abstraction at the C-1 in (91) by base followed by a rearrangement to give the 5H-isomer. Or alternatively, racemization at C-1 in (91) by base to the more stable isomer (90), followed by a slower base induced rearrangement to give the 5H-isomer.

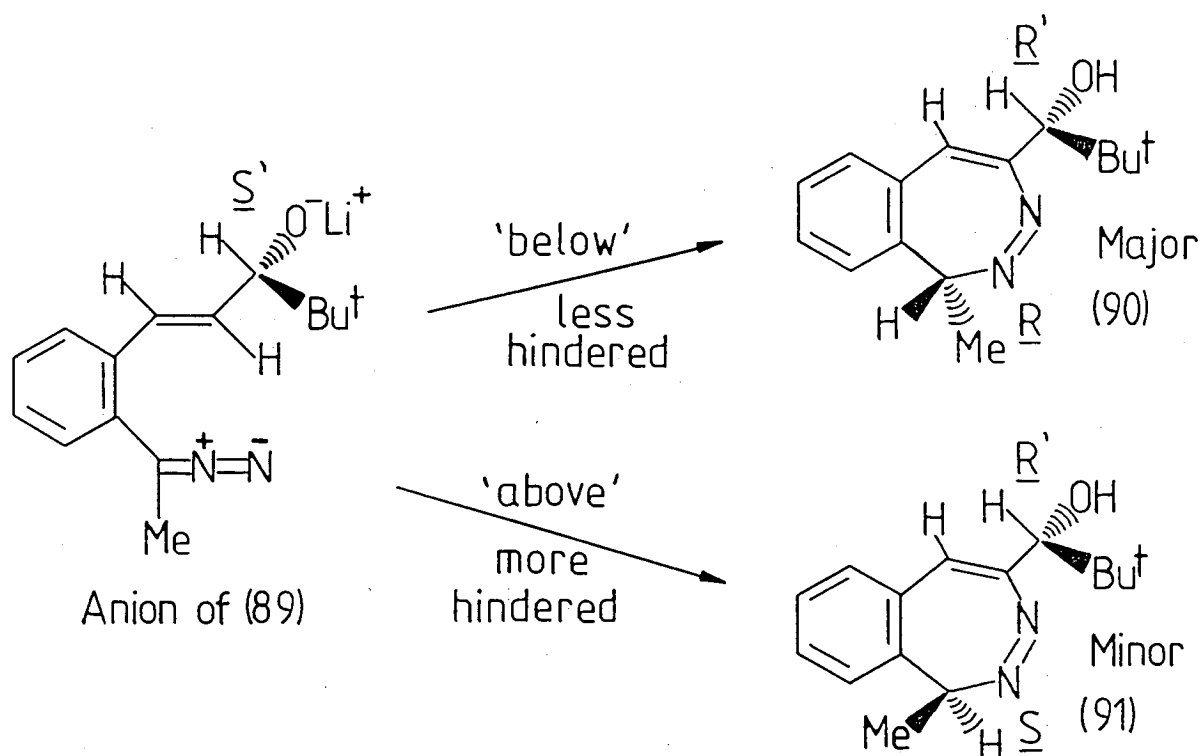
To determine the true pathway, (91) was prepared in high purity [(98%), contained 2% of (90)]. The benzodiazepine was heated to reflux in dimethoxyethane containing butyllithium (1 molar equivalent) and diphenyl ether as an internal standard. The reaction was monitored by h.p.l.c. until virtually all of the isomer (91) had been consumed. It was observed that the percentage of isomer (91) changed from 98 to 4% (percentage on total benzodiazepines), while the level of 5H-isomer rose to 94%. The percentage of (90) remained constant throughout. However, the total amount of the benzodiazepines was found to decrease by two thirds of its original level [assuming that (92) has the same h.p.l.c. response factor as (90)/(91)].

This experiment confirms that the base induced isomerisation of (91) to (92) does not proceed via isomer (90). Also, that the presence an excess of base lowers the yield of the required diastereomers and gives a product ratio which does not truly reflect the effect caused by asymmetric induction

To avoid the based induced isomerization, the reaction was repeated using 1.95 molar equivalents of butyllithium.

The reaction was carried out as before, with h.p.l.c. monitoring of the products formation. After 5h, all of the tosylhydrazone had been consumed. The diastereomer ratio (90):(91) was found to be 84:16 by ^1H n.m.r. and h.p.l.c. (see Appendix II, Diagram 10). None of the 5H-isomer was detected by h.p.l.c. throughout the reaction.

This experiment confirms that when the alkoxide ion is present in the chiral group, the major isomer is preferentially formed (72% d.e.) by attack by the diazo-group at the less hindered face of the alkene in its ground state conformation (Scheme 21).



Scheme 21

1-Methyl-4-(2',2'-dimethyl-1',3'-dioxolan-4yl)-1H-2,3-benzodiazepines (93)/(94).

The diazoalkane (92) was cyclised in the usual fashion. After 5.5h, the reaction the reaction was complete. This was followed by the usual workup. The ratio of the benzodiazepines (93):(94) was found to be 34:66 by ¹H n.m.r. and 36:64 by h.p.l.c. However the products decomposed before separation of the diastereomers could be attempted.

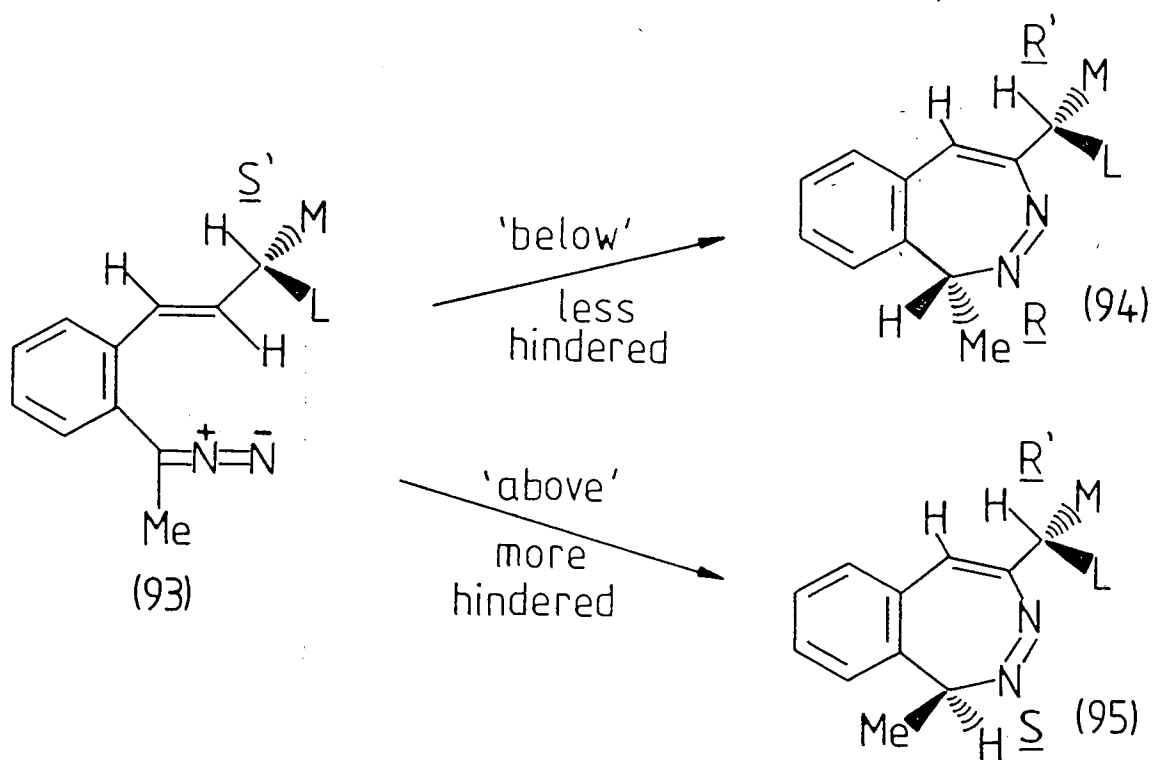
This is a remarkable reversal of face selectivity to that observed when the chiral group contains the intact hydroxyl function. An explanation of this phenomenon is given in Section 2.

1.10. Summary of the stereoselectivity found in the 1,7-electrocyclisation reaction.

The chiral centres discussed in this section can be placed into two categories; those that induce the diazo-group to attack preferentially from the less hindered face of the lowest energy conformation of the reactant [(93) in Scheme 22] and those that induce the diazo-group to attack preferentially from the more hindered face of the lowest energy conformation of the reactant.

The results of the cyclisations of chiral diazo-compounds of the type (93) in Table 1 show that attack from the less hindered face is preferred when the medium sized group M= alkyl group or the alkoxide ion. However, this situation is reversed as shown in Table 2, where M= an alkoxy group, the hydroxyl group or an ester group, that is, attack from the more hindered face is strongly favoured.

The following section will attempt to explain these results using some generalisations established in the work of Houk on related cycloaddition reactions.



Scheme 22

Table 1 Attack on the less hindered face of (93)

L	M	(94):(95)	% d.e.
Ph	Me	55 : 45	10
Bu ^t	O ⁻	85 : 15	70
Bu ^t	Et	63 : 37	26
Bu ^t	Me	58 : 42	16

Table 2 Attack on the more hindered face of (93)

L	M	(94):(95)	% d.e.
Ph	OMe	44 : 56	12
Bu ^t	OMe	8 : 92	84
Bu ^t	OTBDMS	9 : 91	82
Bu ^t	OH	29 : 71	42
Bu ^t	OCOPh	41 : 59	18

Section 2 Explanation of the stereoselectivity found in the 1,7-electrocyclisation reaction.

The experimental results described in the previous section, have shown which diastereomers are favoured in the electrocyclisation reactions. However, they give no direct information about the conformational preferences of the chiral allylic groups in the transition structures leading to products.

Calculations by Houk¹¹⁹ on model geometries for the transition structures for attack of electrophiles on substituted alkenes have shown that despite the different attack angles of the electrophiles, the conformations of the transition structures have certain similarities. Houk has found that the allylic bonds are staggered with respect to partially formed bonds in the transition structure¹²³. Thus, as shown in Figure 1, the attack of a reagent, X, on an unsaturated molecule with an allyl chiral centre can occur from any of six possible staggered conformations.

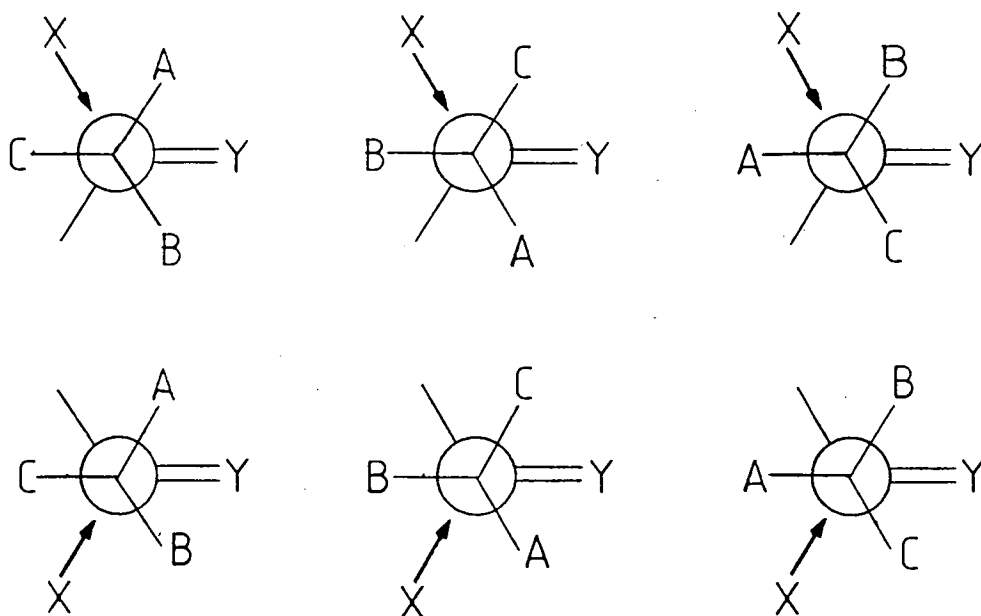


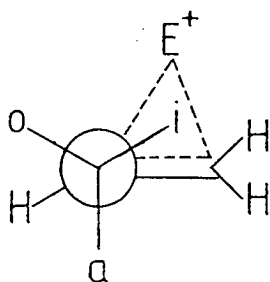
Figure 1

Also, such conformations allow staggering of the partially pyramidalised carbon undergoing attack, with respect to the allylic bonds.

Since the arrangement of allylic bonds appears to be dictated by the forming bond, the exact conformation of the allylic group in the transition state may depend upon the trajectory of attack. Therefore, the lowest energy transition structure leading to products will largely depend upon the staggering, coupled to the direction of attack. In addition to these factors, when the allylic group is chiral, the steric requirements of each distinctly different group must be taken into account. This is further complicated by electronic factors, if an electropositive or electronegative group is present.

Despite, the numerous conformational possibilities suggested by the interactions of the above factors, Houk has rationalised the conformational preferences and has produced some generalisations on the selectivity found in cycloaddition reactions¹¹⁹. These hopefully can be applied to the 1,7-electrocyclisation reaction.

As previously mentioned (see page 51 of this thesis), Houk has stated that an allylic group bearing three groups of different size, will always adopt a staggered conformation with the largest group *L* antiperiplanar to the attacking reagent as shown in (96). The antiperiplanar position being the least crowded and thus the lowest energy conformation for the large group.



a= anti
i='inside'
o='outside'

(96)

The different steric demands placed on 'outside' and 'inside' allylic substituents depends largely on the direction of attack. When the angle of attack is acute [(115) on page 55 of this thesis], the smallest sized group **S** will be 'inside' and the medium sized group **M** will adopt the 'outside' position. When the attack angle is obtuse [(116) on page 55 of this thesis], the medium sized group will adopt the 'inside' position and the small sized group will be in the 'outside' position. On steric grounds these preferred conformations will be the lowest energy conformation for the transition structure.

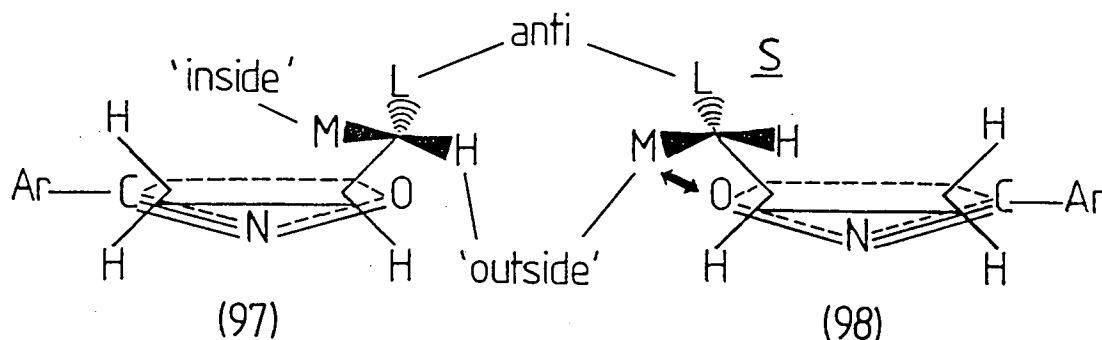
Houk has also discussed the influence of electronic effects on transition structure conformation. An electronegative allylic group favours the 'inside' or 'outside' positions to minimize electron withdrawal from the already electron deficient transition structure. Which position is favoured depends on other factors such as the interactions between the attacking electrophile and the group at the 'inside' or 'outside' positions.

Using the above generalisations, the following sections will attempt to describe the probable preferred transition structures in the 1,7-electrocyclisation and compare the models

with those determined by Houk in the intermolecular nitrile oxide cycloaddition to allylic chiral alkenes.

2.1. M = Alkyl group

Houk in his intermolecular nitrile oxide cycloadditions (NOC) to chiral alkenes^{121,126}, examined the selectivity of chiral substituents containing alkyl groups. A selection is shown in Table 4 on page 68 of this thesis. In the series where M = a methyl group and the size of L was varied, he found that the preferred product was obtained by attack from the more hindered face of the alkene in its ground state conformation. From his transition state model calculations Houk believes that the major product arises from the staggered transition structure (97), which has L anti to the attacking electrophilic group and M to be in the 'inside' position.



This allows M to simultaneously avoid the incoming oxygen on the nitrile oxide and the L-CH₂ repulsion. The minor product is formed when L is anti and M occupies the 'outside' position (98). The almost tetrahedral angle of approach the oxygen in the nitrile oxide brings it into greater conflict with M and as a result, increases the conflict between L and the CH₂. As the size of L increases the more crowded the 'outside' becomes,

thus favouring the 'inside' transition structure (97). This also is confirmed by Cozzi in his work on intramolecular nitrile oxide cycloadditions with his E-alkenes¹⁴⁶.

In the analogous 1,7-electrocyclisation reaction of $\alpha, \beta:\gamma, \delta$ -unsaturated diazoalkanes in which the chiral substituent contains alkyl groups as **M** the medium sized group. We have shown that the major product arises by the approach of the diazo-group from the less hindered face of the alkene in its ground state conformation (**M**=alkyl group in Table 1 on page 81). This is the opposite to what was discussed by Houk in the cycloaddition reactions discussed above.

The degree of selectivity in the 1,7-electrocyclisations was found to differ with the nature of the substituents attached to the chiral group. When **M**= methyl and **L**= phenyl, a 10% d.e. was found, but this increased to 16% d.e. when **L** was changed to tert-butyl.

When **L**= tert-butyl and **M** was varied, it was found that the diastereoselectivity increased with the size of the group:

INCREASING STERIC SIZE ———>

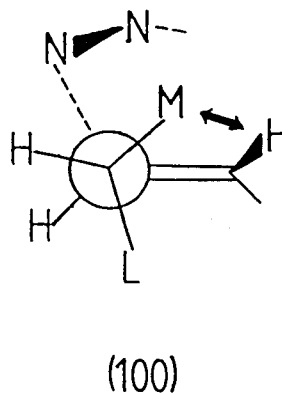
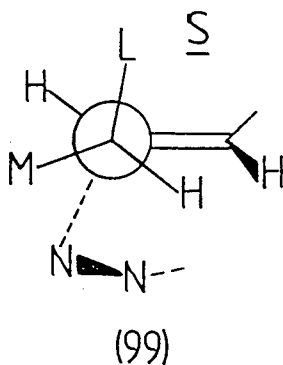
M	Me	Et
% d.e.	10	26

As part of the study, some of the reactions were carried out in solvents of differing polarity. The results (Table 3) show that the diastereoselectivity was largely unaffected by changing solvent polarity.

M	L	Cyclohexane	Dimethoxyethane	Dimethylformamide
		(94):(95)	(94):(95)	(94):(95)
Me	Bu ^t	58 : 42	55 : 45	57 : 43
Et	Bu ^t	63 : 37	62 : 38	61 : 39

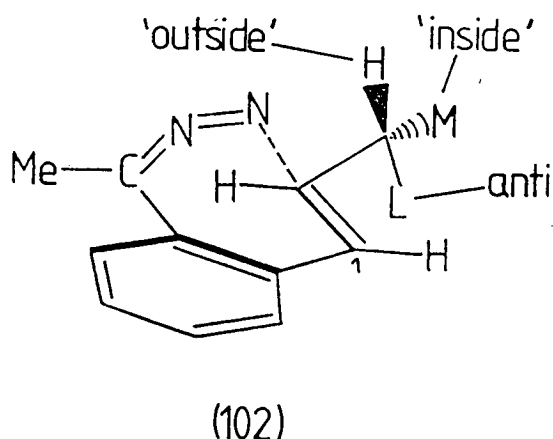
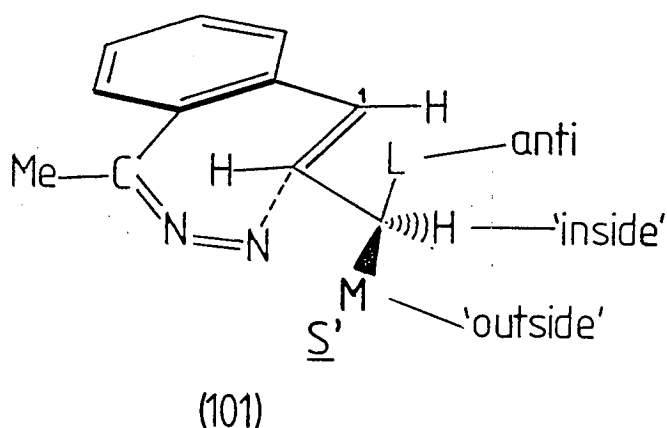
Table 3

From the experimental results and applying some of Houk's generalisations, the following conclusions were made. The preferred transition structures leading to the both products must have the large sized group L antiperiplanar to the incoming diazo-group. The major product is formed when M adopts the 'outside' position as shown in the transition structure (99). Conversely, to obtain the minor isomer the conformation must have M in the 'inside' position as shown in the transition structure (100).



In the 1,7-electrocyclisation of the diazoalkane, it has been established that the molecule will adopt a helical transition structure (see page 38 of this thesis). In such a structure, the angle of attack is less than 109° and the approach of the terminal nitrogen of the diazo-group is not perpendicular to the plane of the double bond, but at an

'obtuse' angle as shown in (101).



Due to this angled approach, interactions between the incoming diazo-group and the **M** group are minimal in both the 'outside' and the 'inside' position. This allows other steric factors to dominate the conformation preference of **M**. When **M** occupies the 'inside' position as in (102), there is a steric interaction between it and the C-1 hydrogen, which results in a higher energy transition structure, than when it occupies the 'outside' position, where it is able to avoid such interactions. In the transition structure (101), the hydrogen is 'inside' and in this position the steric repulsion between it and the C-1 hydrogen is much smaller than the case shown in (102). Therefore, the 'outside' transition structure is lower in energy and is reflected in the selectivity of the reaction, by favouring attack from the less hindered face of the alkene. When the size of the **M** group is increased the less stable (102) is further destabilized, favouring the transition structure (101). This is confirmed by the experimental work.

Recent ab initio calculations of the transition structure geometry for the electrocyclicisation¹⁶⁹ and some molecular

mechanics (MM2) calculations of the relative energies of the transition structure with a methyl group in the 'inside' and the 'outside' positions have been carried out.¹⁷⁰ The calculated energy levels of the six possible staggered conformations (shown for $R^C = \text{Bu}^t, \text{Me}, \text{H}$) shown in Figure 2. The top three, all involve attack of the diazo-group to give the major product, and the bottom three (shown for the S enantiomer) give the minor product. Transition structures (103) and (104) in Figures 2 and 3 are the lowest in energy and therefore the more favoured conformations of the six.

The difference in energy between the two best transition structures (103) and (104) is small (0.23 kcal per mole) and this explains why the diastereoselectivity of this molecule is low. The calculated product ratio using MM2 was (72):(73) 59:41 and was found experimentally to be 58:42. Therefore, these energy calculations therefore, support the theory discussed above.

The poor diastereoselectivity when $L = \text{phenyl}$, is probably due to its small size in comparison to the tert-butyl group. When a small group is used for L , the preference for the transition structure with L in the anti position will be less and there will probably be substantial contributions from the other two staggered transition structures with the phenyl in the 'inside' or the 'outside' positions (for an impression of the other transition structures see Figure 2 and substitute phenyl for tert-butyl).

The diastereoselectivity was found to be unaffected, when the reaction was carried out in solvents of high polarity,

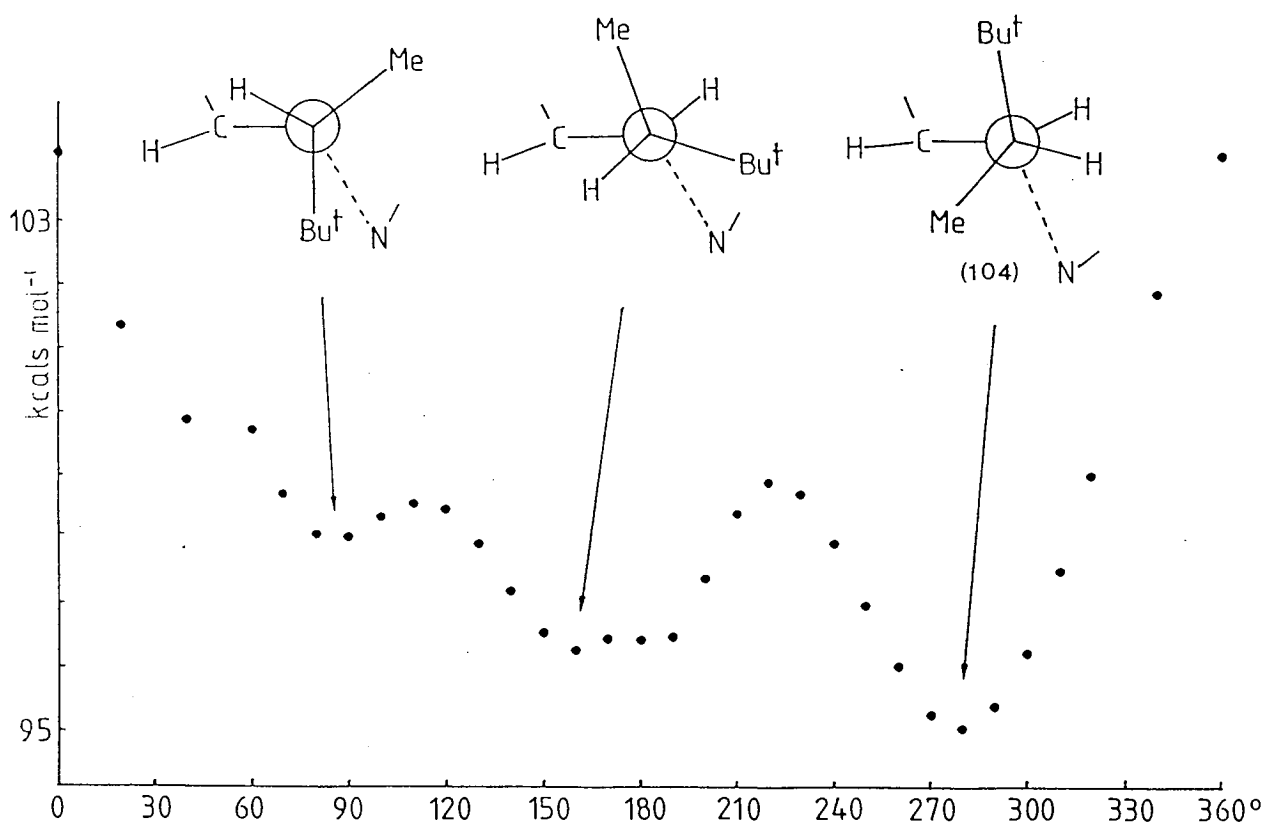
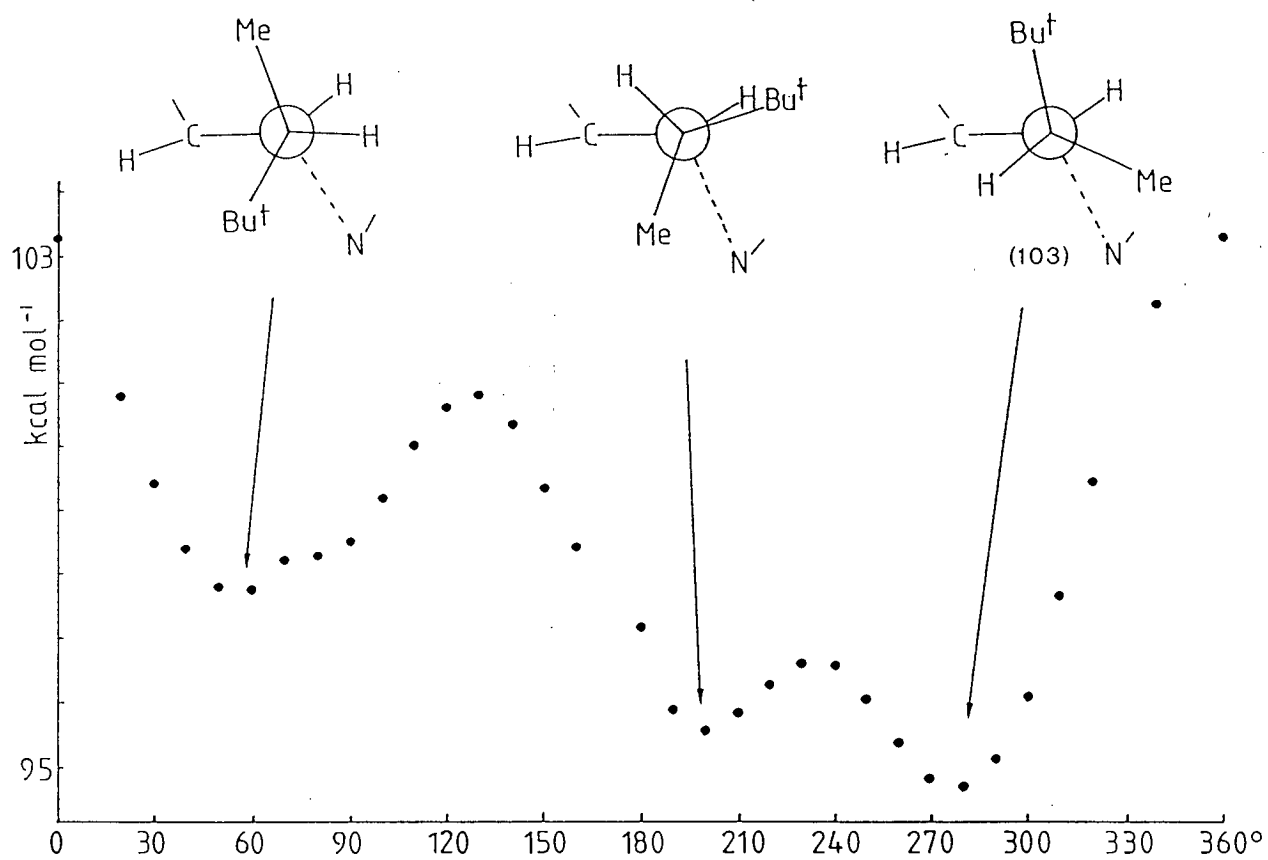
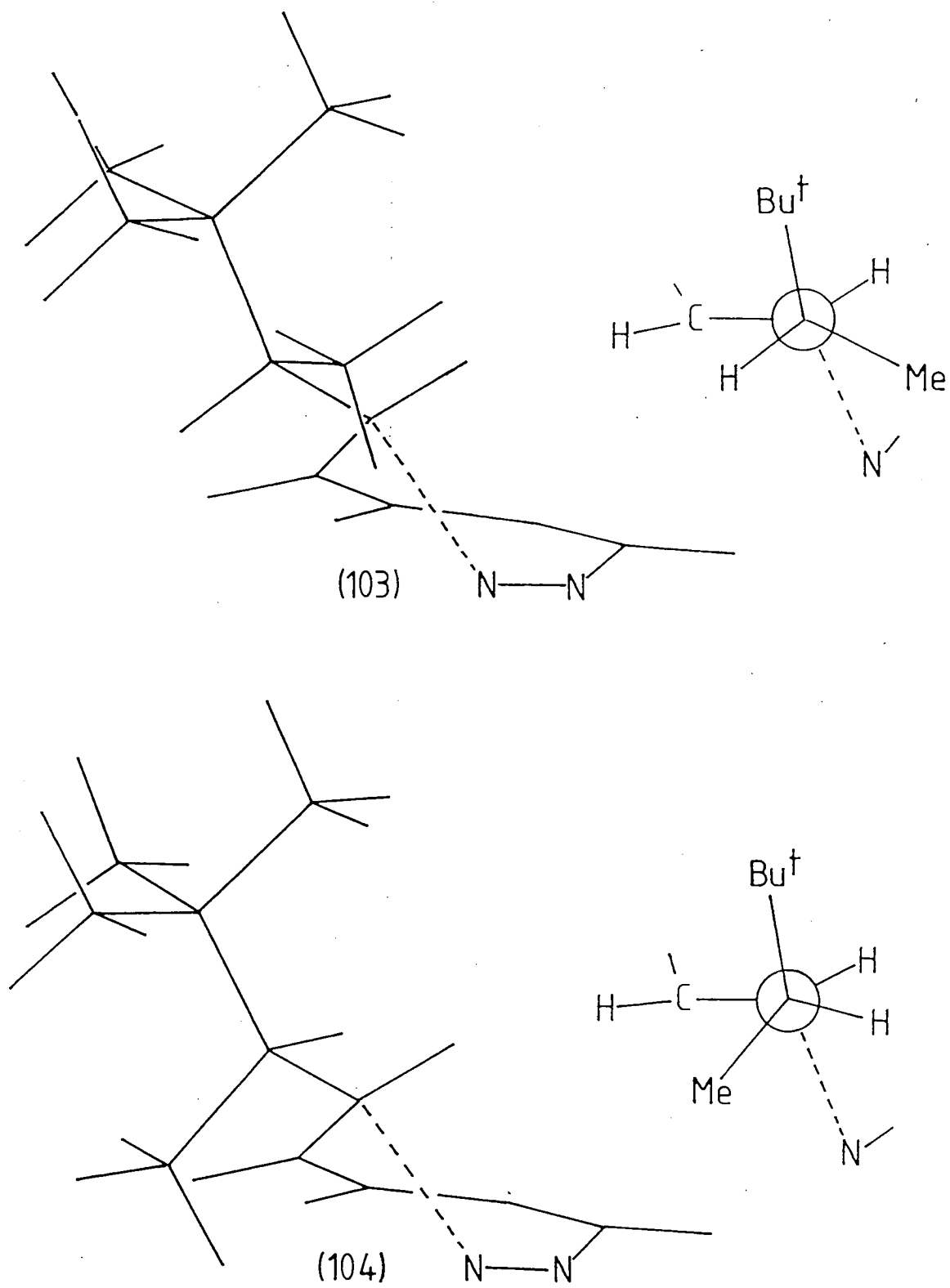


Figure 2

Figure 3

confirming the absence of electronic factors such as dipole-dipole repulsions.

The essential points which emerge from this work on systems in which M is an alkyl group are summarized below:

(i) The facial selectivity is the opposite of that observed by Houk and his intermolecular nitrile oxide cycloaddition reactions as discussed above. In all his results where M= an alkyl group, he found that the preferred product was obtained by attack from the more hindered face of the alkene in its ground state conformation. The preferred conformation of M leading to the major isomer was calculated to be the 'inside' position, which allowed M to simultaneously avoid the incoming oxygen on the nitrile oxide and the R-CH₂ repulsion, as shown in (96).

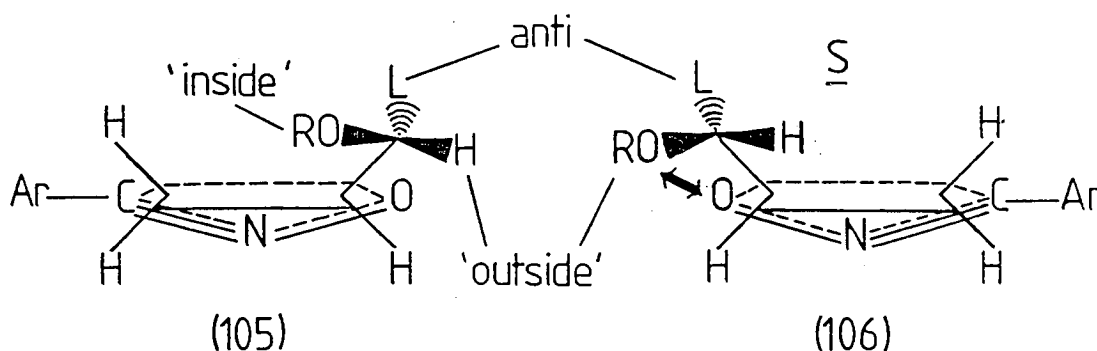
(ii) In the 1,7-electrocyclisation, the angled approach of the diazoalkane is different to the parallel approach of the nitrile oxide. The effect of this is to make the 'outside' position less crowded than the 'inside' and hence the preference is for M to occupy the 'outside' position. This conclusion has been supported by the ab initio calculations and the molecular mechanics (MM2) calculations.

(iii) Despite the differences in the transition structure geometry of the two reactions, it is interesting to note that in both cases increasing the size of M, raises the selectivity. This supports the conclusion that the effect of M in both cases is primarily steric and not electronic, a view which is also supported by the insensitivity of the selectivity to solvent polarity.

2.2. M= Alkoxy group, or an ester group.

In his NOC study, Houk obtained his highest selectivity when a chiral allyl ether was employed¹²⁶ (Table 3 on page 66 of this thesis). In every example where M= alkoxy group, he found that the preferred product was obtained by attack from the more hindered face of the alkene in its ground state conformation. The selectivity was found to improve by increasing the size of the alkyl group, L, in the chiral center. Also, the selectivity was not affected by the nature of the substituent on the allylic oxygen.

From his MM2 calculations, Houk postulated that the selectivity observed in the cycloaddition to chiral allyl ethers, resulted from the alkoxy group preference for the 'inside' position and the alkyl groups preference for the anti position as shown in transition structure (105).



The minor product is formed when L is anti and the alkoxy group occupies the 'outside' position (106). The preference for the 'inside' or the 'outside' position over the anti position is largely an electronic effect. The adoption of either position minimises electron withdrawal from the electron deficient transition structure. However, the preference for

the 'inside' over the 'outside' is as discussed earlier in 2.1, due to the 'outside' position being an unfavourable conformation near the nitrile oxide oxygen resulting in a polar repulsion (replacing the steric repulsion in 2.1) of the alkoxy group away from the alkene plane.

In the 1,7-electrocyclisation reaction, the highest diastereoselectivities of the study were also obtained, when a chiral allyl ether was employed. In each case, the major product arose via the approach of the diazo-group from the more hindered face of the alkene in its ground state conformation (M=alkoxy group in Table 2 on page 81).

The selectivity in the 1,7-electrocyclisation was found to vary with the nature of the substituents attached to the chiral group. When M= methoxy and L = phenyl, a 12% d.e. was found, but this increased to 84% d.e. when L= tert-butyl. This large difference can be attributed again to the smaller size of the phenyl group reducing preference for the transition structure with L in the anti position, allowing contributions from the other two staggered conformations

It was noted that the size of the alkoxy substituent had little effect on the diastereoselectivity. Changing M from methoxy to the sterically larger OTBDMS group did not alter the ratio of products. Clearly, the substituents attached to the oxygen can freely rotate away from any steric interactions and so avoid raising the energy of the transition structure.

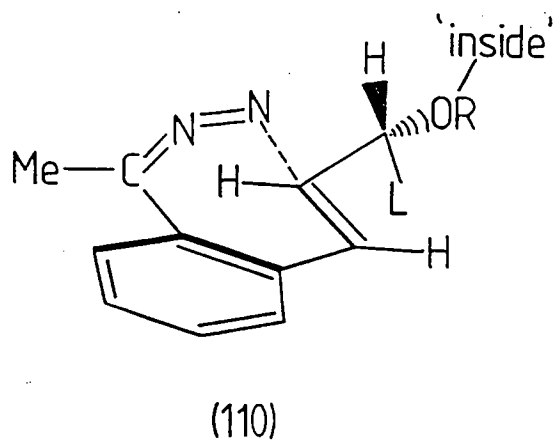
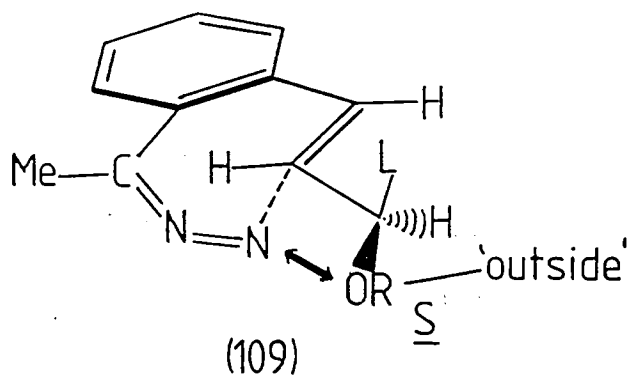
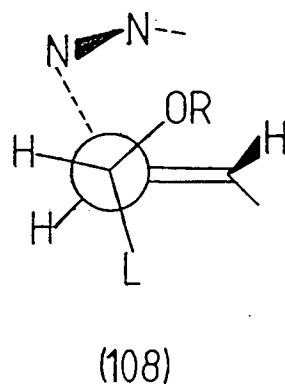
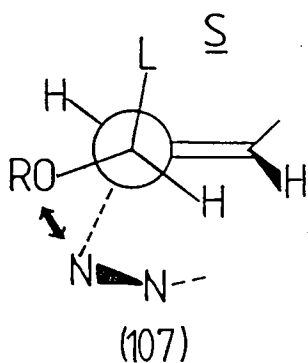
When the reactions were carried out in different solvents, it was observed that increasing solvent polarity reduced the diastereoselectivity found in the reaction (Table 4).

M	L	Cyclohexane Dimethoxyethane Dimethylformamide		
		(94):(95)	(94):(95)	(94):(95)
OMe	Bu ^t	8 : 92	10 : 90	16 : 84
OTBDMS	Bu ^t	9 : 91	11 : 89	12 : 88

Table 4

The experimental results suggest that the preferred transition structure leading to the major isomer must have the **L** antiperiplanar to the incoming diazogroup and the alkoxy group adopting the 'inside' position as shown in the transition structure (108) and (110).

To obtain the minor isomer the conformation must have alkoxy group in the 'outside' position as shown in the transition structure (107) and (109).



This strong preference must be derived from electronic factors. This is from a comparison with the similar shaped, but electronically different chiral groups, where M is an ethyl group. The latter shows a modest preference for the transition structure with the group in the 'outside' position. Clearly, if the facial preference was determined by steric factors alone, then both sterically similar shaped chiral group would have the same preferences for attack.

On electronical orbital grounds, the methoxy group would prefer to be close to the alkene plane to minimize σ^*_{C-O} overlap in the alkene HOMO. It has been calculated using MM2 calculations that for the 'obtuse' angle of attack, the best transition structure (111) leading to minor product, as shown in Figure 4, has the methoxy group closer to the alkene plane than the best transition structure leading to major product (112). Therefore on orbital grounds, the methoxy group should prefer the 'outside' position. However the experimental results have shown that this is not the case. The main reason for the preference for methoxy 'inside', is probably polar repulsion between the oxygen in the 'outside' position and the leading nitrogen in the diazo-group. In the 'inside' transition structure (111), in Figures 4 and 5, it has been shown that the distance between the oxygen and the nitrogen is 3.51Å, whereas in the best 'outside' transition structure (112), in Figures 4 and 5, it is 3.03Å, i.e., considerably closer in the 'outside' transition structure. Furthermore, MM2 calculations indicate that of the 1.75 kcal difference between the two transition structures, about 1.0 kcal is due to electrostatic repulsion between the methoxy oxygen and the

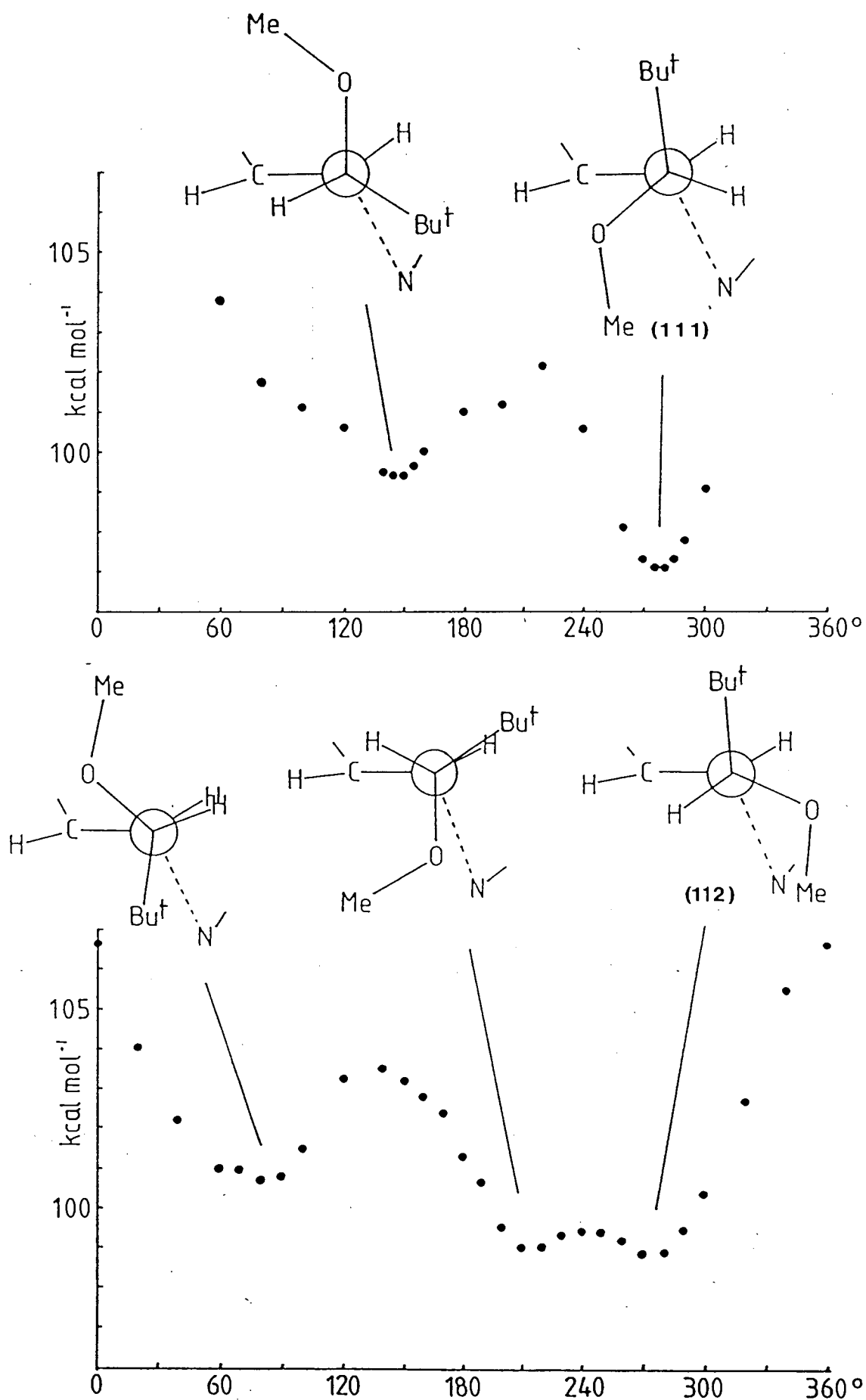
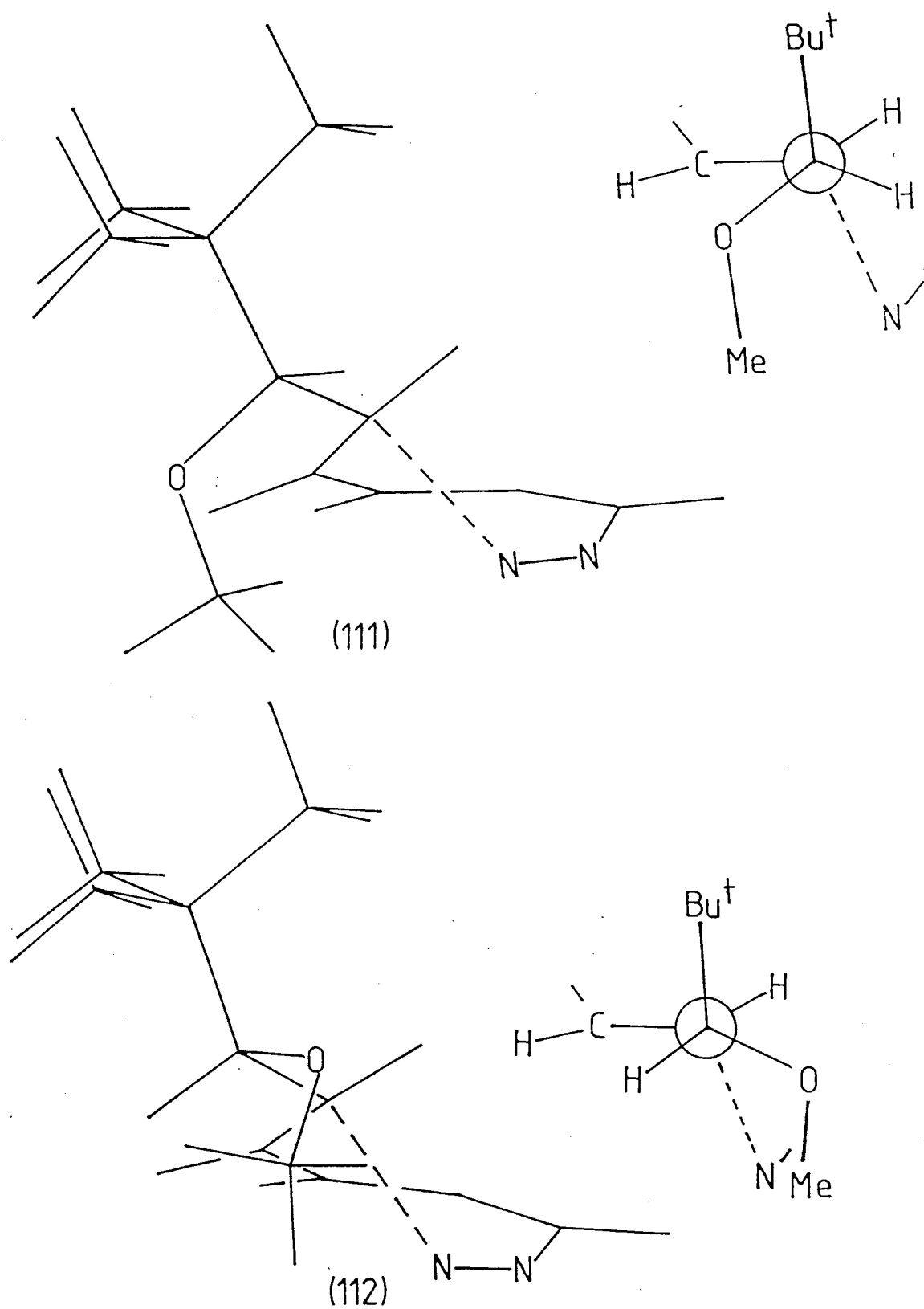


Figure 4

Figure 5

leading nitrogen. This higher energy value caused by the electrostatic repulsion is therefore the deciding factor in the methoxy's preference for the 'inside' position. The calculated product ratio of (78):(79) 7:93, agrees with the experimental ratio of 8:92, upholding the theory above.

Further support is shown by the effect of solvent polarity on the selectivity. The higher the dielectric constant of the solvent, the lower the selectivity (Table 4). This effect must be attributed to the reduction by the solvent of the electrostatic repulsion between the nitrogen and the oxygen of the methoxy group, therefore lowering the energy of the 'outside' transition structure.

The low selectivity observed for the benzoate chiral group can be attributed to the different electronic nature of the ester group. The mesomeric effect in the ester group as shown in the canonical forms in Figure 6 results in a lower electron density on the alkyl-oxygen.



Figure 6

It would therefore be expected that the electrostatic repulsion between the oxygen and the nitrogen of the dipole will in this case be less than in the case of methoxy group. Thus, the 'inside' preference for the ester is less than for the ether group.

The points which emerge from this work are summarized below.

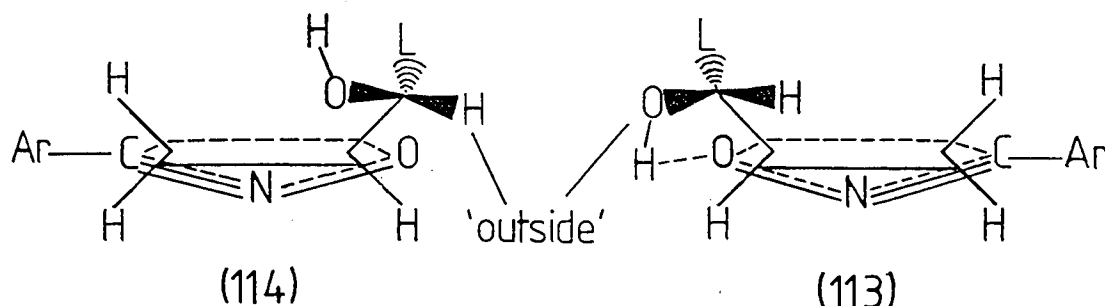
(i) The more hindered face preferences of the chiral allyl ethers in the 1,7-electrocyclisation are in agreement with Houks findings in his NOC work, and also by other workers in similar cycloaddition reactions^{109,138,139,141,142}. The presence of an electronegative group in the chiral centre clearly dominates the selectivity by its avoidance of the 'outside' position. This appears to be due in most part to its polar repulsion by the attacking atom of the 1,3-dipole.

(ii) In the NOC reaction, it was noted that a slightly higher diastereoselectivity (>5% d.e.) was found than in the 1,7-electrocyclisation reaction bearing identical chiral groups. This may be due to the difference in the geometry of the transition structure in the two cases. In the NOC reaction, the alkoxy group in the 'outside' position lies in closer proximity to the oxygen of the incoming nitrile oxide than it does to the nitrogen of the diazo-group in the 1,7-electrocyclisation, due to the angled approach in the latter case. The polar repulsion and hence the 'inside' preference would therefore be expected to be smaller in the 1,7-electrocyclisation reaction.

2.3. M=Hydroxy group or the alkoxide ion.

In the NOC reaction, in every case where M= an hydroxy group, the major product was formed by attack from the least hindered face of the alkene in its lowest energy conformation. Also, the selectivity was found to be low (20-30% d.e.). Houk suggested that this reversal of face selectivity was caused by

hydrogen bonding between the hydroxy group and the nitrile oxide oxygen. This hydrogen bonding by the hydroxy group in the 'outside' position as shown in (113), lowers the energy of the transition structure to a level below that of the transition structure with the hydroxy group in the 'inside' position (114).

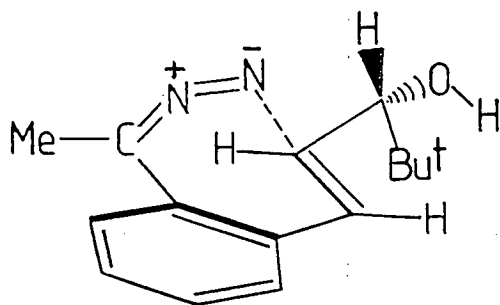


Solvent effects support this proposal; the major isomer selectivity is diminished as the hydrogen bond acceptor capability of the solvent is increased. Other workers^{138,140} have supported this theory.

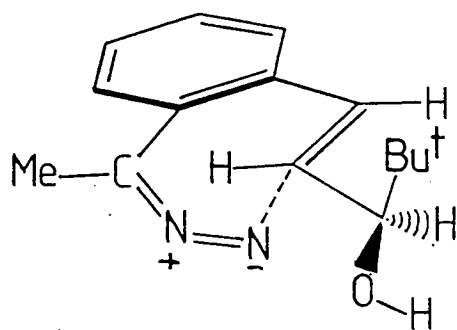
The NOC reaction of a chiral allylic group bearing an alkoxide ion substituent has not been reported in the literature.

The 1,7-electrocyclisation bearing a chiral group with a hydroxy substituent was found to favour the product derived by attack of the diazo-group from the more hindered face of the alkene in its lowest energy conformation. This preference is identical to that of the alkoxy group, however, only a 42% d.e. was found, compared with a 80% d.e. (in dimethoxyethane) when M= methoxy.

Applying Houk's generalisations to the electrocyclicisation, the best transition structures have the hydroxy group occupying the 'inside' as shown in (115), or the 'outside' position (116).



(115)

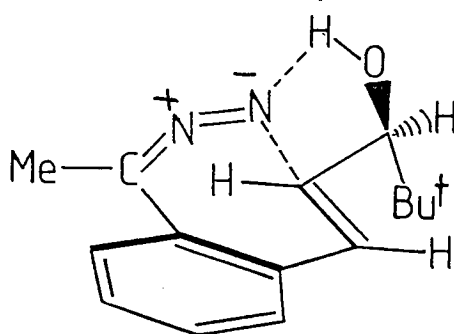


(116)

It was found experimentally, that the major isomer was formed from the 'inside' transition structure (115), and the minor isomer from the 'outside' transition structure (116).

As discussed before in the case M = methoxy, the 'inside' position is preferred because of polar repulsion effects between the oxygen and the leading nitrogen of the diazo-group.

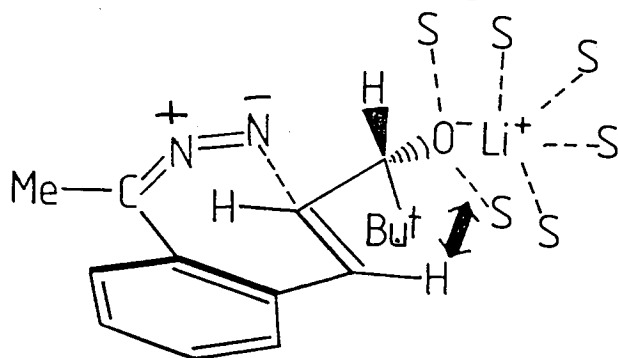
The lower selectivity in the hydroxy case is probably caused by some weak hydrogen bonding between the hydroxy group in the 'outside' position and the nitrogen of the diazo-group, so weakly stabilizing the 'outside' transition structure and lowering the selectivity as shown in (117).



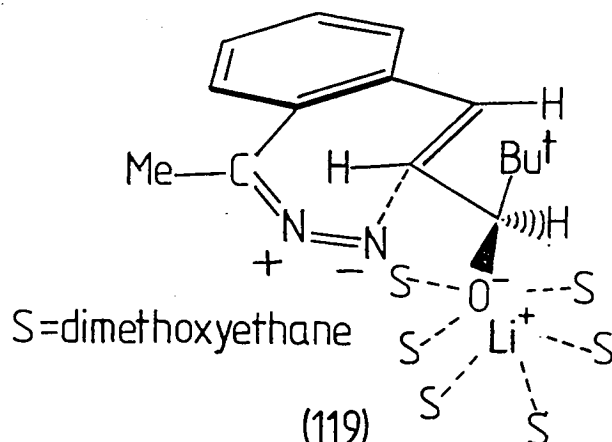
(117)

When the 1,7-electrocyclisation was carried out with two equivalents of base so that the alkoxide ion was formed, it was found that there was a preference for attack on the least hindered face of the alkene in its lowest energy conformation; the opposite face of attack to the hydroxy group. In addition the selectivity was higher (70% d.e.).

To explain this reversal of selectivity, it must be realised that the alkoxide will not be present as a 'naked' anion, but will have in close proximity the lithium counterion. Two explanations are forwarded for this 'outside' preference. First, such an ion-pair will attract a solvent cage which will be held together by strong dipole-dipole attractions. Therefore, the actual steric size of the alkoxide ion will be much larger than anticipated as shown in (118) and (119).



(118)

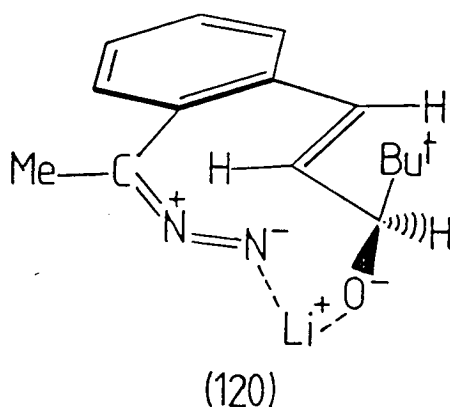


(119)

S=dimethoxyethane

The large steric bulk of this solvated ion-pair will no doubt increase the steric interactions with the C-1 hydrogen, when it occupies the 'inside' position. The conflict becomes so great that the energy of the 'inside' transition structure (118) is greater than that of the 'outside' transition structure (119); the consequence being that the solvated ion-pair will strongly prefer to occupy the 'outside' position. Second, the polar attraction of the lithium cation to the nitrogen of the diazo-group may have a strong stabilizing effect on the 'outside' transition structure as depicted in (120).

Both these effects may occur simultaneously, and if so, their effect on the selectivity would be additive.



2.4. Summary

The selectivity found in the 1,7-electrocyclisation has been tentatively rationalised in the sections above.

The work carried out to date appears to agree with Houk's conclusions derived from calculations on model geometries; that the lowest energy transition structure will largely depend upon the staggering, coupled to the direction of attack.

Our conclusions are that the product forming transition structures are staggered with respect to the partially formed bonds in the transition structure, and that the L group in the allylic chiral substituent will always prefer to be anti to the attacking diazo-group. These assumptions are in agreement with Houk's NOC study, but, because the 1,3-dipoles angles of attack are unlike, there are differences in the 'inside'/'outside' preference of the M group. In the NOC reaction where M= alkoxy or an alkyl group, the 'inside' transition structure dominates; the exception being M= hydroxy group where hydrogen bonding between the hydroxy in the 'outside' and the oxygen in the nitrile oxide stabilises the transition structure.

In the 1,7-electrocyclisation, the more angled approach of the diazo-group probably reduces the steric repulsion effects when M= alkyl group, and the 'outside' transition structure is weakly preferred. However, this angled approach does not diminish electrostatic repulsion effects and when M= alkoxy, the 'inside' transition structure is dominant, because of the strong polar repulsion between the methoxy oxygen and the leading nitrogen in the diazo-group. This repulsion is weakened when M= benzoate or hydroxy ; the former by mesomeric effects, the latter by the formation of a weak hydrogen bond between the hydroxy group and the leading nitrogen.

The presence of an alkoxide ion as the M group reverses this preference, favouring the 'outside' position. It has been forwarded that weak bonds between the leading nitrogen and the lithium cation stabilise this transition structure.

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Symbols and Abbreviations

m.p.	melting point
b.p.	boiling point
t.l.c.	thin-layer chromatography
g.l.c.	gas-liquid chromatography
m.p.l.c.	medium pressure liquid chromatography
h.p.l.c.	high performance liquid chromatography
n.m.r.	nuclear magnetic resonance
Hz	hertz
MHz	megahertz
br.	broad
s; d; t;	singlet; doublet; triplet;
q; m	quartet; multiplet
quat.	quaternary
J	coupling constant
δ	chemical shift
i.r.	infrared
M^+	mass of molecular ion
m/z	mass to charge ratio
h; mins; sec.	hours; minutes, seconds
p.p.m.	parts per million
mol	moles
mmol	millimoles
L	litres
ml	millilitres
THF	tetrahydrofuran
DME	dimethoxyethane
DMF	dimethylformamide
v/v	volume/volume
w/w	weight/weight

INSTRUMENTATION AND TECHNIQUES

Nuclear Magnetic Resonance Spectroscopy

^1H N.m.r. spectra were obtained using; (i) Varian EM360 (60MHz), Joel-PMX-60 (60MHz) and Bruker WP80 (80MHz) spectrometers for routine samples; (ii) Bruker WP 80 (80MHz), WP200 (200MHz) and WH360 (360MHz) spectrometers for spectra of new compounds and high resolution spectra. ^{13}C N.m.r. spectra were obtained using the Bruker WP200 (50.32MHz) spectrometers. Spectra are recorded as values for solutions in deuteriochloroform unless otherwise stated. The spectrometers were operated by Mr. J.R.A. Millar, Mr. L.H. Bell, Miss H. Grant, Dr. D. Reed and Dr. I.H. Sadler.

Mass Spectrometry

Mass spectra were obtained using an Associated Electrical Industries MS902 spectrometer operated by Miss E. Stevenson, or a Kratos MS50 spectrometer operated by Mr. A. Taylor.

Infrared Spectroscopy

Liquid samples were examined as thin films and solid samples as nujol mulls or as melts, on sodium chloride plates on a Perkin-Elmer 781 spectrometer. Spectra were calibrated with the polystyrene peak at 1603 cm^{-1} .

Elemental Analysis

Micro analyses for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba 1106 elemental analyser operated by Mrs E. McDougall.

Melting Points.

Melting points were determined using a Gallenkamp melting point apparatus. The values given are uncorrected.

Gas-Liquid Chromatography

A Pye Series 104 Chromatograph using a flame ionisation detector and nitrogen carrier gas gave analytical chromatograms. The column used throughout had an internal diameter of 4 mm and length 1 metre and was packed with a methyl silicone oil (OV1) supported on 80-100 mesh celite (2.5% w/w).

Medium Pressure Liquid Chromatography¹⁷¹

Preparative separations were carried out using Merck silica gel 60 (40-60 μ m), tap-fill packed in glass columns [250 x 15 mm, 1000 x 15 mm, 1000 x 25 mm (Quickfit Ltd.)] fitted with solvent-resistant connector and tubing (Jobling Corning) and safety valve (50 p.s.i. Nupro Gauge Co. Ltd.). The samples were preadsorbed onto silica gel and packed into small (250 x 15 mm) 'pre columns'. The eluting solvent systems were based on petroleum ether 40/60 with varying amounts of ether or ethyl acetate. The solvent systems was delivered at a flow rate of 5-20 ml min⁻¹ from a diaphragm pump (Metering Pumps Ltd.), depending on column size. The eluant was collected in an automatic fraction collector (Central Ignition Co. Ltd.) and the fractions were examined by t.l.c. or by h.p.l.c..

High Performance Liquid Chromatography

Analytical chromatograms were obtained using a solvent

metering pump (model 110A) and sample injection valve (model 210) supplied by Altex Scientific Inc. A variable wavelength ultraviolet monitor (CE212) supplied by Cecil Instruments was used throughout as the peak detector, at the wavelength of 254 nm.

Prepacked h.p.l.c. columns were used, supplied by 'h.p.l.c. technology' using Hypersil 5 (5 μ m) packed in a 100 x 5 mm column for normal phase; Hypersil 5 SAS (5 μ m) packed in a 100 x 5 mm column for reverse phase. The porous graphite carbon column (100 x 5 mm) was supplied by Prof. J. Knox of the University of Edinburgh. Standard h.p.l.c. grade solvents were used throughout.

Dry Column Flash Chromatography¹⁷²

This was carried out using silica gel (Fluka silica gel G; for thin layer chromatography) in porosity 3 cylindrical sinters (30 x 70 mm). The samples were applied as solutions in the minimum volume of eluant or by preadsorption onto silica gel (Fluka G) from DCM solutions, added to the top of the column and packed down onto the column after initial passage of eluant. The components were eluted by adding successive portions (25 to 50 ml) of solvent mixtures (based on petroleum ether 40/60 and varying amounts of ether or ethyl acetate) and allowing the column to be sucked dry by a water vacuum pump after each portion. The fractions were examined by t.l.c. or by h.p.l.c..

Drying

Solid samples for elemental analysis or for reactions

requiring anhydrous conditions were dried in a drying pistol (A. Gallenkamp & Co. Ltd.) under high vacuum over phosphorus pentoxide. Liquid samples were dried by distillation or by the method below. Anhydrous magnesium sulphate was used to dry all organic solutions and for complete removal of traces of water, anhydrous calcium sulphate was used.

Glassware was dried in an oven for 4 h at 140°C, then purged with dry nitrogen while hot.

Purification of Solvents

'Super dry' ethanol was prepared as described by Vogel (Method 1) and stored over molecular sieve 4Å.

Cyclohexane and 1,2-dimethoxyethane were freshly distilled from calcium hydride as required.

Dimethylformamide was passed through a glass column packed with alumina (Laporte Industries, Grade H 100/200 Mesh) and distilled.

Tetrahydrofuran was freshly distilled from calcium hydride and lithium aluminium hydride.

Diethyl ether and benzene were dried by storage over sodium wire.

Acetone was dried by storage over molecular sieve 4Å.

Pyridine was dried as described by Vogel and stored over potassium hydroxide pellets.

Thin Layer Chromatography

This was carried out on silica (Merck Kieselgel 60g) containing 0.5% Woelm fluorescent green indicator, unless

otherwise stated that alumina was used (0.3 mm layer of neutral aluminium oxide 60G, Type E). Components in the developed chromatogram were detected by their quenching of fluorescence under ultra-violet light, and their staining by iodine vapour.

Gravity Column Chromatography

This was carried out on alumina (Laporte Industries, Grade H 100/200 Mesh) prepared to 6% w/w deactivation.

Flash Chromatography¹⁷³

This was carried out using silica gel 60 (40-63 μ m), tap-filled 18" glass columns (10, 20 or 30 mm) fitted with Teflon stopcock and topped with a 24/40 glass Quickfit joint, carrying a flow controller. The samples were preadsorbed onto silica gel 60 (40-63 μ m) from DCM solutions. Eluant was passed through the column at a rate of 2" min^{-1} and the eluant collected in 50 ml fractions, in 20 x 150 mm test-tubes.

PREPARATION OF STARTING MATERIALSPREPARATION OF P-TOLUENESULPHONYLHYDRAZONES1) Preparation of 1-acetyl-2-(E/Z-3'-phenylbut-1'-enyl) benzene tosylhydrazonesa) 2-Bromobenzyl bromide

2-Bromotoluene (100 g, 0.585 mole) was heated to reflux and bromine (93.5 g, 0.585 mole) was added over 1 h. The mixture was refluxed for a further 0.25 h, cooled and left overnight. The crude product was distilled to give

2-bromobenzyl bromide as a colourless oil (116 g, 80%),

b.p. 79-82°C at 0.5 mmHg (lit.¹⁷⁴, b.p. 129°C at 19 mmHg);

δ_H (60MHz; $CDCl_3$) 4.53 (2H, s), 7.58-6.80 (4H, m, aromatic).

b) 2-Bromobenzyltriphenylphosphonium bromide

2-Bromobenzyl bromide (100 g, 0.4 mole) was added to a solution of triphenylphosphine (110.2 g, 0.42 mole) in benzene (500 ml) and refluxed for 0.5 h. After cooling, the precipitate was filtered and washed with petrol (2 x 50 ml) giving white crystals of 2-bromobenzyltriphenylphosphonium bromide (193 g, 94%), m.p. 195-197°C (lit.¹⁷⁵, m.p. 195-197°C); δ_H (80MHz; $CDCl_3$) 5.58 (2H, d, J 14.2Hz), 7.1-7.9 (19H, m, aromatic).

c) 1-Bromo-2-(3'-phenylbut-1'-enyl)benzene as an E/Z mixture (1)/(2)

A solution of sodium ethoxide [(0.072 mole) from sodium (1.66 g)] in super dry ethanol (50 ml) was added over 0.5 h at room temperature to a stirred mixture of (+-)-2-phenylpropionaldehyde (9.4 g, 0.07 mole) and 2-bromobenzyltriphenylphosphonium bromide (35.8 g, 0.07 mole)

in super dry ethanol (50 ml). The mixture was stirred at room temperature for 1 h, then the solvent removed in vacuo. The residue was partitioned between DCM (30 ml) and water (30 ml). The aqueous layer ^{was} separated and the organic layer washed with water (2 x 10 ml), dried and the solvent removed in vacuo.

Chromatography (alumina, petrol) gave

1-bromo-2-(3'-phenylbut-1'-enyl)benzene (17.2 g, 86%)

containing the E and Z isomers in the ratio (1):(2) 61:39

(g.l.c., 200°C) (Found: C, 66.6; H, 5.23%; M^+ , 288.0338.

$C_{16}H_{15}Br$ requires C, 66.9; H, 5.23%; M, 288.0338); δ_H (200MHz; $CDCl_3$) 1.42 (d, J 6.9Hz, Z-Me), 1.54 (d, J 7.0Hz, E-Me), 3.76 (1H, m, E and Z-3'-H), 5.97 (dd, J 10.5 and 6.6Hz, Z-2'-H), 6.36 (dd, J 15.8 and 6.6Hz, E-2'-H), 6.53 (d, 10.5Hz, Z-1'-H), 6.85 (d, J 15.8Hz, E-1'-H), 7.0-7.6 (9H, m, aromatic).

The conversion of the Z-isomer to the E-isomer was attempted by dissolving the oil in n-heptane (50 ml) containing iodine (100 mg) and refluxing for 24 h. G.l.c. indicated no change in the isomer ratio.

Chromatography (silica, petrol) of the oil gave no separation of the isomers.

d) 2-(3'-phenylbut-1'-enyl)benzaldehyde as an E/Z mixture
(3)/(4)

Butyllithium (11.3 ml, 1.50 M solution in hexane, 0.017 mole) was added dropwise with stirring to 1-bromo-2-(3'-phenylbut-1'-enyl)benzene (1)/(2) (4.4 g, 0.015 mole) in THF (10 ml) at -78°C under dry nitrogen. The mixture was stirred for 0.5 h at -78°C, then dry DMF (2.25 g, 0.031 mole) in THF (5 ml) was added dropwise over 0.25 h. The

mixture was stirred for 2 h at -78°C , then left to stir overnight at room temperature. The mixture was poured into 25% w/v aqueous ammonium chloride solution (50 ml), the organic phase separated and the aqueous phase extracted with DCM (2 x 25 ml). The combined organic layers were washed with water (20 ml), dried and the solvent removed in vacuo to give a brown oil. Chromatography, eluting with petrol:ether (98:2) gave an E/Z mixture of 2-(3'-phenylbut-1'-enyl)benzaldehyde (3)/(4) as a yellow oil (2.0 g, 57%), (E:Z ratio 67:33) (Found: m/z 236.1212. $\text{C}_{17}\text{H}_{16}\text{O}$ requires m/z 236.1201); δ_{H} (200MHz, CDCl_3) 1.36 (d, J 7.0Hz, Z-Me), 1.53 (d, J 6.9Hz, E-Me), 3.71 (1H, m, E and Z-3'-H), 6.10 (dd, J 11.3 and 6.8Hz, Z-2'-H), 6.34 (dd, J 15.7 and 6.8Hz, E-2'-H), 6.54 (d, J 11.3Hz, Z-1'-H), 7.14-7.96 (m, aromatic and E-1'-H), 10.25 (s, Z-CHO), 10.29 (s, E-CHO); i.r. (film) 2820, 2720 (aldehyde C-H), and 1690 cm^{-1} (C=O).

e) 1-Hydroxyethyl-2-(3'-phenylbut-1'-enyl)benzene as an E/Z mixture (5)/(6)

A Grignard reagent was prepared by the addition of methyl iodide (0.66 g, 4.65 mmole) to magnesium (0.78 g, 4.85 mmole) in dry ether (2 ml). A solution of 2-(3'-phenylbut-1'-enyl)benzaldehyde (3)/(4) (1.0 g, 4.23 mmole) in dry ether (5 ml) was added dropwise with stirring over 0.25 h at 0°C then stirred for 2 h. The mixture was poured into 25% w/v aqueous ammonium chloride (25 ml), the organic phase separated and the aqueous layer extracted with ether (2 x 10 ml). The combined ether layers were washed with water (2 x 5 ml), dried and the solvent removed in vacuo to

give the E/Z mixture of 1-hydroxyethyl-2-(3'-phenylbut-1'-enyl)benzene (5)/(6) as a colourless oil (1.0 g, 94%), (Found: m/z 252.2525. $C_{18}H_{20}O$ requires m/z 252.2514); δ_H (200MHz; $CDCl_3$) 1.34-1.55 (6H, m, E and Z-Me), 2.00 (1H, br s, OH), 3.70 (1H, m, E and Z-3'-H), 5.05 (q, J 6.5Hz, Z-H), 5.19 (q, J 6.6Hz, E-H), 5.93-6.03 (m, Z-H), 6.26 (dd, J 15.6 and 6.6Hz, E-2'-H), 6.58 (d, J 11.4Hz, Z-1'-H), 6.75 (d, J 15.6Hz, E-1'-H), 7.12-7.6 (9H, m, aromatic); i.r. (film) 3330 cm^{-1} (OH); m/z 252(12%), 234(20), 219(43), 208(14), 193(14), 147(64), 134(74), 115(24), 105(100), 91(42).

f) 1-Acetyl-2-(3'phenylbut-1'-enyl)benzene as an E/Z mixture (7)/(8)

Chromium trioxide (0.9 g, 9 mmole) was added during 0.25 h with stirring and ice cooling to pyridine (9.0 ml). 1-Hydroxyethyl-2-(3'-phenylbut-1'-enyl)benzene (5)/(6) (0.76 g, 3 mmole) was added and the mixture left stirring overnight. Ether (45 ml) was added and the dark brown precipitate filtered off. Water (50 ml) was added to the filtrate, the ether layer separated, and the water layer extracted with ether (2 x 10 ml). The combined ether layers were washed with water (10 ml), dried and the solvent removed in vacuo to give a yellow oil (0.63 g). Chromatography, eluting with petrol:ether (95:5) gave the E/Z mixture of 1-acetyl-2-(3'phenylbut-1'-enyl)benzene as a pale yellow oil (0.51 g, 68%), [E:Z ratio (7):(8) 67:33] (Found: C, 87.2; H, 7.39. $C_{18}H_{18}O$ requires C, 87.36; H, 7.25%); δ_H (200MHz; $CDCl_3$) 1.33 (d, J 7.0Hz, Z-Me), 1.48 (d, J 7.0Hz, E-Me), 2.50 (s, Z-Me), 2.54 (s, E-Me), 3.64-3.71 (1H, m), 5.89 (dd, J 11.3 and 6.6Hz, Z-2'-H), 6.24 (dd, J 15.8

and 6.8Hz, E-2'-H), 6.76 (d, J 11.4Hz, Z-1'-H), 6.94 (dd, J 15.9H, E-1'-H), 7.1-7.7(9H, m, aromatic); i.r. (film) 1685cm^{-1} (C=O).

g) 1-Acetyl-2-(3'-phenylbut-1'-enyl)benzene tosylhydrazone as an E/Z mixture (9)/(10)

A solution of 1-acetyl-2-(3'-phenylbut-1'-enyl)benzene (7)/(8) (0.70 g, 2.9 mmole) in ethanol (2 ml) was warmed to 35°C and added to a solution of p-toluenesulphenylhydrazide (0.55 g, 2.9 mmole) in ethanol (8 ml) at 35°C , containing one drop of concentrated hydrochloric acid. The mixture was stirred for 0.25 h and then left standing overnight. T.l.c. indicated a mixture of E and Z-tosylhydrazones. The solvent was removed in vacuo and chromatography by m.p.l.c., eluting with petrol:ether (55:45) gave

(i) 1-acetyl-2-(E/Z-3'-phenylbut-1'enyl)benzene tosylhydrazone(9) as a white solid (0.27 g, 23%), m.p. $82.0 - 85.0^{\circ}\text{C}$ (Found: C, 71.0; H, 6.24; N, 6.77. $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$ requires C, 71.6; H, 6.24; N, 6.72%); δ_{H} (200MHz; CDCl_3) spectra similar to (b); i.r. (nujol) 3200 cm^{-1} (NH).

ii) 1-acetyl-2-(E/Z-3'-phenylbut-1'enyl)benzene tosylhydrazone(10) as a green solid (0.54 g, 46%), m.p. 95°C (decomp.) (Found C, 71.7; H, 6.28; N, 6.75. $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$ requires C, 71.6; H, 6.24; N, 6.72%); δ_{H} (200 MHz; CDCl_3) 1.23 (d, J 7.0Hz, Z-Me), 1.38 (d, J 7.0Hz, Z-Me), 1.38 (d, J 7.0Hz, E-me), 2.01 (s, E-Me=N), 2.04 (s, Z-MeC=N), 2.40 (s, E-tosylMe), 2.42 (s, Z-tosylMe), 3.52 (1H, m, 3'-H), 5.64 (t, J 10.5Hz, Z-2'H), 6.10 (dd, J 15.7 and 6.3Hz, E-2'H), 6.30 (d, J 11.5Hz, Z-1'-H), 6.44 (d, J 15.7Hz, E-1'-H)

7.08 - 7.42 (11H, m, aromatic), 8.0 (3H, m, aromatic and NH);
i.r. (nujol) 3205 cm^{-1} (NH).

h) Attempted preparation of (7)/(8) from (1)/(2)

A general method suggested by Eberle¹⁷⁶ was used.

A Grignard reagent was prepared by the addition of 1-bromo-2-(3'-phenylbut-1'-enyl)benzene(1)/(2) (2.9 g, 10 mmole) in THF (3 ml) to magnesium (0.25 g, 10.3 mmole) with stirring and under dry nitrogen. The mixture was heated to reflux for 1 h, then cooled to 0°C .

Freshly distilled acetyl chloride (1.57 g, 20 mmole) in THF (3 ml) was cooled to -78°C , under dry nitrogen. The Grignard reagent was added dropwise over 0.5 h, with vigorous stirring at -78°C , then left to stir overnight. The mixture was poured into ice:25% w/v aqueous ammonium chloride solution (25 ml) (1:1) with stirring. The organic phase was separated and the aqueous phase extracted with DCM (2 x 10 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (10 ml), water (2 x 10 ml), dried and the solvent removed in vacuo to give an orange oil (2.5 g). T.l.c. of the oil indicated a four component mixture. Dry column flash chromatography, eluting with petrol:ether (100:0 to 70:30) gave:

(i) colourless oil (1.27 g). G.l.c. (200°C) indicated product was a mixture of (1)/(2) and the hydrocarbon (11/12).

(ii) colourless oil (0.12 g).

(iii) an orange oil (0.70 g); δ_{H} (80MHz; CDCl_3) 1.20 - 2.00 (m), 2.04 (s), 3.40 (t, J 6.4Hz), 4.16 (t, J 6.1Hz),

7.2 - 7.4 (m, aromatic); i.r. (film 1740 cm^{-1} ; m/z 322 (30%),

266 (40), 223 (80), 208 (88), 207 (100), 146 (95).

Compound not the expected product (7)/(8).

(iv) colourless oil (0.08 g).

i) 1-Hydroxyethyl-2-(3'-phenylbut-1'-enyl)benzene as an E/Z mixture (5)/(6)

A Grignard reagent was prepared by the addition of 1-bromo-2-(3'-phenylbut-1'-enyl)benzene(1)/(2) (2.9 g, 10 mmole) in THF (3 ml) to magnesium (0.25 g, 10.3 mmole) with stirring and under dry nitrogen. The mixture was stirred at 40°C for 0.3 h, then cooled to -10°C.

Acetaldehyde (0.45 g, 10.3 mmole) in THF (1 ml) was added dropwise over 0.5 h, the temperature kept below -5°C. The mixture was stirred for 0.5 h, then poured into crushed ice. Dilute hydrochloric acid (10 ml) was added with stirring. The mixture was extracted with ether (3 x 10 ml). The combined ether layers were dried and the solvent removed in vacuo to give a red oil (2.2 g). Dry column flash chromatography, eluting with petrol:ether (100:0 to 70:30) gave two oils:

(a) colourless oil (1.28 g). G.l.c. (200°C) indicated product was a mixture of (1)/(2) and the hydrocarbon (11)/(12).

(b) E/Z-mixture of 1-hydroxyethyl-2-(3'-phenylbut-1'-enyl)benzene as a colourless oil (0.14 g, 6%); δ_{H} (80MHz; CDC13) 1.35 - 1.55 (6H, m, Me's), 2.0 (1H, brs, OH), 3.70 (1H, m), 5.10 (1H, m) 5.93 - 6.75 (2H, m, alkenic), 7.12 - 7.60 (9H, m, aromatic); i.r. (film) 3350 cm^{-1} (OH).

j) E/Z-3-Phenylbut-1-enylbenzene (11)/(12)

Butyllithium (0.61 ml, 1.50 M solution in hexane, 0.91 mmole) was added dropwise with stirring to

1-bromo-2-(3'-phenylbut-1-enyl)benzene (1)/(2) (0.25 g, 0.87 mmole) in THF (5 ml) at -78°C under dry nitrogen. The mixture was left to stir for 0.5 h at -78°C , then water:THF (5 ml) (50:50) was added over 0.1 h. The mixture was stirred for 0.25 h at -78°C then allowed to reach room temperature. 25% w/v aqueous ammonium chloride solution (5 ml) was added and the organic phase separated. The aqueous layer was extracted with DCM (2 x 10 ml). The combined organic layers were washed with water (5 ml), dried and the solvent removed in vacuo to give E/Z-3-phenylbut-1-enylbenzene (11)/(12) as a colourless oil (0.15 g, 83%), (Found m/z 208.1252. $\text{C}_{16}\text{H}_{16}$ requires m/z 208.1255); δ_{H} (80MHz; CDCl_3) 1.46 (d, J 7.0Hz, Me), 1.55 (d, J 7.0Hz, Me), 3.95 (1H, m), 6.40 (2H, m, alkenic), 7.24 - 7.45 (10H, m, aromatic); m/z 208 (6%), 193 (8), 128 (7), 115 (48), 102 (17), 91 (27) 78 (100).

k) Attempted preparation of (4) from (1)

A lithium acetate solution was prepared by butyllithium (3.83 ml, 1.50 M solution in hexane, 5.74 mmole) added to glacial acetic acid (0.31 g, 5.22 mmole) in THF (8 ml) at 0°C ¹⁵³.

1-Bromo-2-(3'-phenylbut-1-enyl)benzene (1)/(2) (0.50 g, 1.74 mmole) in THF (5 ml) was cooled to -78°C and butyllithium (1.22 ml, 1.5 M solution in hexane, 1.83 mmole) was added with stirring over 0.1 h under dry nitrogen. The mixture was stirred for 0.3 h, then the lithium acetate solution (4 ml, 1.83 mmole) was added dropwise over 0.15 h. The mixture was stirred overnight at room temperature. The usual work up gave a colourless oil (0.4 g). G.l.c. (200°C) indicated 60% was hydrocarbon (11)/(12) and 18% (1)/(2).

- 1) 1-Acetyl-2-(3'-phenylbut-1'-enyl)benzene (7)/(8) as an E/Z mixture from (1)/(2) in two steps.

Butyllithium (7.3 ml, 1.50 M solution in hexane, 11 mmole) was added dropwise with stirring to 1-bromo-2-(3'-phenylbut-1'-enyl)benzene (1)/(2) (2.87 g, 10 mmole) in THF (25 ml) at -78°C under dry nitrogen. The mixture was stirred for 0.5 h at -78°C , then acetaldehyde (0.46 g, 0.10 mole) in THF (5 ml) was added dropwise over 0.5 h at -78°C . The mixture was left to stir overnight at room temperature, then poured into 25% w/v aqueous ammonium chloride solution (50 ml). The organic phase separated and the aqueous phase extracted with DCM (3 x 25 ml). The combined organic layers were washed with water (2 x 25 ml), dried and the solvent removed in vacuo to give a yellow oil (2.5 g). T.l.c. indicated the alcohol product (5)/(6) was present as well as a larger proportion of (11)/(12) and (1)/(2). The crude product was oxidised to the ketone (7)/(8) by the procedure described in experiment (1.f.). The usual work up and dry column flash chromatography, eluting with petrol:ether (90:10) gave the E/Z-mixture of 1-acetyl-2-(3'-phenylbut-1'-enyl)benzene (7)/(8) as a colourless oil (0.48 g, 19%); δ_{H} (200MHz; CDCl_3) 1.33 (d, J 7.0Hz, Z-Me), 1.48 (d, J 7.0Hz, E-Me), 2.50 (s, Z-MeC=O), 2.54 (s, E-MeC=O), 5.89 (dd, J 11.3 and 6.5Hz, Z-2'-H), 6.24 (dd, J 15.8Hz and 6.7Hz, E-2'-H), 6.76 (d J 11.3Hz, Z-1'-H), 6.94 (d, J 15.8Hz, E-1'-H), 7.11 - 7.72 (9H, m, aromatic); i.r. (film) 1685 cm^{-1} (C=O).

2) Preparation of 2-(E-3'-phenylbut-1'-enyl)benzaldehyde tosylhydrazone

a) Separation of the isomers (1) and (2)

A solution of the E/Z mixture of 1-bromo-2-(3'-phenylbut-1'-enyl)benzene (1)/(2) (33 g) in petrol (30 ml) was cooled to 0°C. The white solid of the Z-isomer (2) was filtered and washed with ice cold petrol (10 ml). The filtrate was shown by g.l.c. (200°C) to contain the isomers (1) and (2) in the ratio 84:16. Petrol (25 ml) was distilled off and the solution cooled slowly to -10°C. The white solid was filtered and washed with ice cold petrol (5 ml). The solvent in the filtrate was removed in vacuo to yield a colourless oil (18.5 g) containing the isomers (1) and (2) in the ratio 90:10. Careful distillation yielded pure 1-bromo-2-(E-3'-phenylbut-1'-enyl)benzene (1) (14.4 g), b.p. 140 - 142°C at 0.5 mmHg (Found: C, 67.0; H, 5.29%; M^+ , 288.0334. $C_{16}H_{15}Br$ requires C, 66.9; H, 5.26%; M , 288.0338); δ_H (200MHz; $CDCl_3$) 1.53 (3H, d, J 7.0Hz, Me), 3.72 (1H, m, J 6.9Hz), 6.32 (1H, dd, J 15.8 and 6.6Hz, 2'-H), 6.85 (1H, d, J 15.8Hz, 1'-H), 7.0 - 7.6 (9H, m, aromatic); m/z 288 (22%), 286 (27), 273 (16), 245 (14), 207 (12), 192 (31), 155 (14), 134 (16), 118 (100), 105 (70).

The white solid of the Z-isomer (2) was recrystallised from ice cold petrol to give white crystals of 1-bromo-2-(Z-3'-phenylbut-1'-enyl)benzene (2) (9.0 g), m.p. 65 - 67°C (Found C, 66.9; H, 5.27. $C_{16}H_{15}Br$ requires C, 66.9; H 5.26%); δ_H (80MHz; $CDCl_3$) 1.36 (3H, d, J 6.9Hz, Me), 3.75 (1H, m, J 6.9Hz, 3'-H),

5.90 (1H, dd, J 11.2 and 10.3Hz, 2'-H),
6.47 (1H, d, J 11.2Hz, 1'H), 7.04 - 7.64 (9H, m, aromatic).

b) 2-(E-3'-phenylbut-1'-enyl)benzaldehyde (3)

Butyllithium (29 ml, 1.50 M solution in hexane, 0.044 mole) was added dropwise with stirring to 1-bromo-2-(E-3'-phenylbut-1'-enyl)benzene (1) (11.0 g, 0.038 mole) in THF (40 ml) at -78°C under dry nitrogen. The mixture was left stirring for 0.5 h at -78°C , then dry DMF (5.8 g, 0.08 mole) in THF (10 ml) was added dropwise over 0.5 h. The mixture was stirred for 2 h at -78°C , then left to stir overnight at room temperature. The mixture was poured into 25% w/v aqueous ammonium chloride solution (150 ml), the organic phase separated and the aqueous phase extracted with DCM (3 x 50 ml). The combined organic layers were washed with water (25 ml), dried and the solvent removed in vacuo to give a yellow oil (9.4 g). Flash chromatography, eluting with petrol: ether (99:1 to 98:2) gave 2-(E-3'-phenylbut-1'-enyl)benzaldehyde (3) as a colourless oil (7.9 g, 86%), (Found: m/z 236.1212. $\text{C}_{17}\text{H}_{16}\text{O}$ requires m/z 236.1201); δ_{H} (80MHz; CDCl_3) 1.50 (3H, d, J 7.0Hz, Me), 3.73 (1H, m), 6.32 (1H, dd, J 15.7 and 6.8Hz, 2'-H), 7.16 - 7.87 (10H, m, aromatic H and 1'-H), 10.28 (1H, s, CHO); i.r. (film) 2820, 2720 (aldehyde C-H), and 1690 cm^{-1} (C=O); m/z 236 (5%), 221 (7), 203 (18), 192 (39), 178 (28), 132 (73), 131 (100), 118 (80), 115 (35), 105 (70).

A 2,4-dinitrophenylhydrazone was prepared and recrystallised from ethanol, m.p. $168 - 169.5^{\circ}\text{C}$

(Found: C, 66.0; H, 4.83; N, 13.4. $C_{23}H_{20}O_4N_4$ requires C, 66.3; H, 4.84; N, 13.45%).

c) 2-(E-3'-phenylbut-1'-enyl)benzaldehyde tosylhydrazone (13)

A solution of 2-(E-3'-phenylbut-1'-enyl)benzaldehyde (3) (1.0 g, 4.2 mmole) in ethanol (2 ml) was warmed to 35°C and added to a solution of p-toluenesulphenylhydrazide (0.86 g, 4.6 mmole) in ethanol (10 ml) at 35°C, containing 2 drops of concentrated hydrochloric acid. The mixture was stirred for 0.25 h and left standing overnight, then placed in a freezer for 24 h. The white crystals were filtered off and recrystallised to give 2-(E-3'-phenylbut-1'-enyl)benzaldehyde tosylhydrazone (13) (1.26 g, 73%), m.p. 146 - 146.5°C (from ethanol) (Found: C, 71.4; H, 5.98; N, 6.94. $C_{24}H_{24}N_2O_2S$ requires C, 71.26; H, 6.00; N, 6.92%); δ_H (200MHz; $CDCl_3$) 1.44 (3H, d, J 7.0Hz, Me), 2.38 (3H, s, tosyl Me), 3.63 (1H, m, J 7.0Hz) 6.15 (1H, dd, J 15.5 and 7.0Hz, 2'-H), 6.75 (1H, d, J 15.7Hz, 1'-H), 7.15 - 7.9 (13 H, m, aromatic), 8.08 (1H, s, CH=N), 8.47 (1H, s, N-H); i.r. (nujol) 3220 cm^{-1} (N-H).

3) Preparation of 1-acetyl-2-(E-3'-phenyl-1'-enyl)benzene tosylhydrazones

a) 1-Hydroxyethyl-2-(E-3'-phenylbut-1'-enyl)benzene (5)

This was prepared by the method described in experiment (1.e.) using 2-(E-3'-phenylbut-1'-enyl)benzaldehyde (3) (2.36 g, 0.01 mole). The usual work up gave 1-hydroxyethyl-2-(E-3'-phenylbut-1'-enyl)benzene (5) as a colourless oil (2.43 g, 96%), (Found m/z 252.1515. $C_{18}H_{20}O$ requires m/z 252.1514); δ_H (80MHz; $CDCl_3$) 1.33 - 1.68 (6H, m,

Me's), 1.90 (1H, brs, OH) 3.52 - 3.86 (1H, m), 5.19 (1H, q, J 6.4Hz), 6.22 (1H, dd, J 15.6 and 6.6Hz, 2'-H), 6.75 (1H, d, J 15.7Hz, 1'-H), 7.09 - 7.57 (9H, m, aromatic); i.r. (film) 3330 cm^{-1} (OH); m/z 252 (12%), 234 (20), 219 (43), 208 (14), 193 (14), 178 (6), 147 (64), 134 (74), 105 (100).

b) 1-Acetyl-2-(E-3'-phenylbut-1'-enyl)benzene (7)

This was prepared by the method described in experiment (1.f.) using 1-hydroxyethyl-2-(E-3'-phenylbut-1'-enyl)benzene (5) (1.75 g, 6.9 mmole). The usual work up and dry column flash chromatography, eluting with petrol:ether (97:3) gave 1-acetyl-2-(E-3'-phenylbut-1'-enyl)benzene (7) as a yellow oil (0.87 g 50%); δ_{H} (80MHz; CDCl_3) 1.5 (3H, d, J 7.0Hz, Me), 2.54 (3H, s, Me C=O), 3.69 (1H, m, 3'-H), 6.24 (1H, dd, J 15.8 and 6.8Hz, 2'-H), 7.0 (1H, d, J 15.8Hz, 1'-H), 7.18 - 7.65 (9H, m, aromatic); i.r. (film) 1685 cm^{-1} (C=O); m/z 242 (17%), 216 (24), 201 (46), 164 (25), 144 (100), 130 (34), 114 (55), 105 (45).

A 2,4-dinitrophenylhydrazone was prepared and recrystallised from ethanol, m.p. $103.5 - 105^{\circ}\text{C}$ (Found: C, 66.65; H, 5.09; N, 12.9. $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4$ requires C, 66.9; H, 5.10; N, 13.0%).

c) 1-Acetyl-2-(E-3'-phenylbut-1'enyl)benzene tosylhydrazone (14)/(15)

This was prepared by the method described in experiment (1.g.) using 1-acetyl-2-(E-3'-phenylbut-1'enyl)benzene (1.13 g, 4.5 mmole). T.l.c. indicated a mixture of E and Z-tosylhydroazones (14/15). The solvent was removed in vacuo and chromatography by m.p.l.c., eluting with

petrol:ether (55:45) gave two white solids. These were recrystallised to give

(i) 1-acetyl-2-(E-3'-phenylbut-1'enyl)benzene tosylhydrazone (14) (0.88 g, 44%), m.p. 94 - 95.5°C (from benzene/petrol 60 - 80) (Found: C, 71.6; H, 6.23; N, 6.74. $C_{25}H_{26}N_2O_2S$ requires C, 71.75; H, 6.26; N, 6.70%); i.r. (nujol) 3200 cm^{-1} (NH).

(ii) 1-acetyl-2-(E-3'-phenylbut-1'enyl)benzene tosylhydrazone (15) (0.44g, 23%), m.p. 104.5 - 105.5°C (from benzene/petrol 60 - 80) (Found: C, 71.6; H, 6.24; N, 6.72. $C_{25}H_{26}N_2O_2S$ requires C, 71.75; H, 6.26; N, 6.70%); δ_H (80MHz; $CDCl_3$) 1.37 (3H, d, J 7.0Hz, Me), 2.00 (3H, s, Me C=N), 2.40 (3H, s, tosyl Me), 3.52 (1H, m, J 7.0 and 6.3Hz, 3'-H), 6.10 (1H, dd, J 15.7 and J 6.3Hz, 2'-H), 6.44 (1H, d, J 15.7Hz, 1'H), 7.04 - 7.95 (14H, m, aromatic and NH); i.r. (nujol) 3205 cm^{-1} (NH).

4) Attempted preparation of

2-(E-3'-phenylbut-1'-enyl)benzophenone tosylhydrazone

a) 2-(E-3'-phenylbut-1'-enyl)benzhydrol (16)

A Grignard reagent was prepared by the addition of bromobenzene (1.21 g, 7.7 mmole) to magnesium (0.19 g, 7.7 mmole) in dry ether (8 ml). A solution of 2-(E-3'-phenylbut-1'-enyl)benzaldehyde (3) (1.67 g, 7 mmole) in dry ether (8 ml) was added dropwise with stirring over 0.3 h at 0°C and then 1 h at room temperature. The mixture was poured into 25% w/v aqueous ammonium chloride solution (30 ml), the organic phase separated and the aqueous phase extracted with DCM (2 x 10 ml). The combined organic layers were washed with

water (5 ml), dried and the solvent removed in vacuo to give 2-(E-3'-phenylbut-1'-enyl)benzhydrol (16) as a colourless oil (2.15 g, 98%), (Found m/z 314.1677. $C_{23}H_{22}O$ requires m/z 314.1671); δ_H (80MHz; $CDCl_3$) 1.35 (3H, d, J 7.0Hz, Me), 2.23 (1H, br s, OH), 3.35 (1H, m, 3'-H), 6.00 (1H, s), 6.12 (1H, dd, J 15.5 and 6.2Hz, 2'-H), 6.61 (1H, d, J 15.6Hz, 1'-H), 7.0 - 7.55 (14H, m, aromatic); i.r. (film) 3360 cm^{-1} (OH); m/z 314 (16%), 209 (53), 196 (39), 181 (19), 154 (100), 147 (69), 142 (37), 131 (50), 105 (92).

b) 2-(E-3'-phenylbut-1'-enyl)benzophenone (17)

This was prepared by the method described in experiment (1.f.) using 2-(E-3'-phenylbut-1'-enyl)benzhydrol (16) (1.9 g, 6 mmole). The usual workup and dry column flash chromatography, eluting petrol:ether (97:3) gave 2-(E-3'-phenylbut-1'-enyl)benzophenone (17) as a yellow oil (1.0 g, 56%), (Found m/z 312.1519. $C_{23}H_{20}O$ requires m/z 312.1514); δ_H (80MHz; $CDCl_3$) 1.27 (3H, d, J 7.0Hz, Me), 3.47 (1H, m, 3'-H), 6.08 - 6.58 (2H, m, alkenic), 6.99 - 7.85 (14H, m, aromatic); m/z 312 (2%), 283 (19), 239 (36), 221 (25), 220 (98), 207 (99), 194, (56), 181 (73), 165 (46), 152 (57), 115 (25), 105 (100).

c) Attempted preparation of

2-(E-3'-phenylbut-1'-enyl)benzophenone tosylhydrazone (18)

A solution of 2-(E-3'-phenylbut-1'-enyl)benzophenone (17) (0.88 g, 2.8 mmole) in ethanol (1 ml) was added to a solution of *p*-toluenesulphenylhydrazide (2.1 g, 11 mmole) in ethanol (10 ml), containing 10 drops of concentrated hydrochloric acid. The mixture was heated to reflux for 3.5 h, cooled and the

solvent removed in vacuo to give a brown oil. The oil was dissolved in DCM (30 ml) and washed with water (5 x 10 ml), dried and the solvent removed in vacuo to give a yellow oil (2.5 g). T.l.c. of the oil indicated a 3 component mixture. Dry column flash chromatography, eluting with petrol:ether (75:25) gave:

- (i) yellow oil (0.48 g). Recovered starting material (17).
- (ii) white solid (1.13 g), m.p. 47.0 - 49.5°C; δ_{H} (80MHz; CDCl_3) 1.24 (d, J 4.8Hz) 1.34 (d, J 7.0Hz), 1.70 (m), 2.40 (s), 2.55 (m), 2.40 (s), 2.55 (m) 7.1 - 8.0 (m, aromatic); i.r. (nujol) 3220 cm^{-1} (NH). Attempts to recrystallise the solid gave only oils.

5) Preparation of

1-acetyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene tosylhydrazone

a) Diethyl (2-bromobenzyl)phosphonate (19)

2-Bromobenzylbromide (187.4 g, 0.75 mole) was added dropwise to triethylphosphite (166.2 g, 1.0 mole) at 150°C over 1 h. The byproduct ethyl bromide was collected by distillation during the addition. The mixture was then heated to 160°C for 4 h. After cooling, excess triethylphosphite was removed in vacuo to give a yellow oil (288 g). The crude reaction mixture was distilled to yield diethyl (2-bromobenzyl)phosphonate (19) as a colourless oil (218 g, 94%), b.p. 130 - 134°C at 0.01 mmHg; (Found: C, 42.7; H, 5.2%; M^+ , 307.9976. $\text{C}_{11}\text{H}_{16}\text{BrO}_3\text{P}$ requires C, 43.0; H, 5.25%; M , 308.0001); δ_{H} (200MHz; CDCl_3) 1.18 (6H, t, J 7Hz, Me),

3.33 (2H, d, J 22Hz, P-CH), 3.98 (4H, q, J 7Hz), 7.03 - 7.51 (4H, m, aromatic); i.r. (film) 1255 cm^{-1} (P=O).

b) 2,3,3-Trimethylbutanal

This was prepared by the method of Meyer and Walkup¹⁵⁴ by the methylation of methyl-3,3-dimethylbutanoate (27 g, 0.21 mole) to give methyl-2,3,3-trimethyl-butanoate (77%). This ester was then reduced by lithium aluminium hydride to 2,3,3-trimethylbutanol (90%) and oxidised by the Swern method. Distillation yielded 2,3,3-trimethylbutanal (64%), b.p. $127 - 129^{\circ}\text{C}$ (lit.¹⁷⁷, 50°C at 18 mmHg).

c) 1-Bromo-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (20)

A solution of lithium diisopropylamide was prepared by the addition of butyllithium (52 ml, 1.35 M solution in hexane, 0.07 mole) to diisopropylamine (7.8 g, 0.077 mole) in THF (20 ml) at 0°C , under dry nitrogen. The lithium diisopropylamide solution was added dropwise over 0.5 h to diethyl (2-bromobenzyl)phosphonate (19) (21.5 g, 0.07 mole) in the THF (70 ml) with stirring at -40°C , under dry nitrogen. The reaction mixture was stirred at -40°C for 0.75 h, then allowed to warm up to 0°C . 2,3,3-Trimethylbutanal (7.3 g, 0.063 mole) in THF (50 ml) was then added with stirring and left for 1 h at 0°C , then 2 h at 40°C . The solvent was removed in vacuo and the residue partitioned between DCM (100 ml) and 10% w/v aqueous ammonium chloride (100 ml). The organic phase was separated and the aqueous phase extracted with DCM (3 x 50 ml). The combined organic layers were washed with water (2 x 50 ml) and dried. Removal of the solvent in vacuo gave a clear oil (18 g) which was separated by chromatography (alumina,

petrol) to give

1-bromo-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (20)
(14.8 g, 88%), (Found m/z 268.0655. $C_{14}H_{19}Br$ requires m/z 268.0651); δ_H (200MHz; $CDCl_3$) 0.93 (9H, s), 1.06 (3H, d, J 6.9Hz, 3'-Me) 2.15 (1H, m, 3'-H), 6.09 (1H, dd, J 15.6 and 9.0Hz, 2'H), 6.66 (1H, d, J 15.6Hz, 1'H), 7.01 - 7.55 (4H, m, aromatic); m/z 268 (9%), 266 (8), 211 (23), 130 (51), 128 (15), 57 (100).

d) 2-(E-3',4',4'-Trimethylpent-1'-enyl)benzaldehyde (21)

A Grignard reagent was prepared by the addition of a solution of

1-bromo-2-(E 3',4',4'-trimethylpent-1'-enyl)benzene (20)
(10.7 g, 0.04 mole) in THF (40 ml) to magnesium (1.07 g, 0.044 mole) with stirring and under dry nitrogen. The temperature was maintained between 15 - 20°C during the addition, then left to stir for 0.5 h at 15°C and 1 h at room temperature. The mixture was cooled to 10°C and dry DMF (6.6 g, 0.09 mole) in THF (40 ml) was added dropwise over 0.25 h, then left to stir overnight at room temperature. The mixture was poured into 25% w/v aqueous ammonium chloride solution, (100 ml), the organic phase separated and the aqueous phase extracted with DCM (3 x 50 ml). The combined organic layers were washed with water (2 x 50 ml) and dried. The solvent was removed in vacuo to yield a yellow oil (9.0 g), which was distilled to give
2-(E-3',4',4'-trimethylpent-1'-enyl)benzaldehyde (21), (7.8 g, 90%), b.p. 93 - 96°C at 0.01 mmHg (Found: C, 83.0; H, 9.30%; M^+ , 216.1512. $C_{15}H_{20}O$ requires C, 83.0; H, 9.30%; M , 216.1514); δ_H (80MHz; $CDCl_3$) 0.95 (9H, s), 1.07 (3H, d, J

7Hz, 3'-Me), 2.16 (1H, m, 3'-H), 6.07 (1H, dd, J 15.7 and 8.9Hz, 2'-H), 7.11 (1H, d, J 15.7Hz, 1'-H), 7.26 - 7.85 (4H, m, aromatic), 10.03 (1H, s, CHO); i.r. (film) 2740 (aldehyde C-H), and 1700 cm^{-1} (C=O); m/z 216 (16%), 161 (9), 160 (68), 145 (100), 129 (15), 115 (28), 91 (30), 77 (15).

e) 1-Hydroxyethyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene
(22)

A Grignard reagent was prepared by the addition of methyl iodide (5 g, 0.035 mole) to magnesium (0.78 g, 0.032 mole) in dry ether (40 ml). A solution of 2-(E-3',4',4'-trimethylpent-1'-enyl)benzaldehyde (21) (6.2 g, 0.028 mole) in dry ether (70 ml) was added dropwise with stirring over 1 h at 0°C , and the mixture stirred for 1.5 h. The mixture was poured into 25% w/v aqueous ammonium chloride (100 ml), the organic phase separated and the aqueous phase extracted with ether (4 x 50 ml). The combined organic layers were washed with water (2 x 50 ml) and dried. The solvent was removed in vacuo to give

1-hydroxyethyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (22) as a colourless oil (6.48 g, 99%), (Found m/z 232.1826.

$\text{C}_{16}\text{H}_{24}\text{O}$ requires m/z 232.1827; δ_{H} (80MHz; CDCl_3) 0.91 (9H, s), 1.04 (3H, d, J 6.8Hz, 3'-Me), 1.46 (3H, d, J 6.4Hz, Me), 2.33 (1H, brs, OH), 2.11 (1H, m), 5.20 (1H, q, J 6.4Hz), 5.98 (1H, dd, J 15.6, 8.8 and 1Hz, 2'-H), 6.63 (1H, d, J 15.6Hz, 1'-H), 7.15 - 7.56 (4H, m, aromatic); i.r. (film) 3340 cm^{-1} (OH); m/z 232 (15%), 175 (12), 158 (84), 143 (100), 129 (50), 115 (45), 103 (12).

A 3,5-dinitrobenzoate derivative was prepared and

recrystallised from isopropanol, m.p. 106.5 - 107°C

(Found: C, 64.9; H, 6.25; N, 6.45. $C_{23}H_{26}N_2O_6$ requires C, 64.8; H, 6.15; N, 6.55%).

f) 1-Acetyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (23)

Chromium trioxide (7.8 g, 0.077 mole) was added during 0.25 h with stirring and ice cooling to pyridine (80 ml). 1-Hydroxyethyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (22) (6.21 g, 0.027 mole) was added, the mixture stirred at 0°C for 0.5 h and then allowed to stir at room temperature overnight. Ether (500 ml) was added and the brown precipitate filtered off and washed with ether (200 ml). The ether solution was washed with water (200 ml) and the solvent removed in vacuo to give an orange oil (6.1 g). Distillation yielded 1-acetyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (23) as a pale yellow oil (5.6 g, 91%), b.p. 110 - 112°C at 0.05 mmHg (Found: C, 83.5; H, 9.9. $C_{16}H_{22}O$ requires C, 83.45; H, 9.6%) (Found m/z 230.1674. $C_{16}H_{22}O$ requires m/z 230.1670); δ_H (80MHz; $CDCl_3$) 0.90 (9H, s), 1.04 (3H, d, J 6.8Hz, 3'-Me), 2.15 (1H, m), 2.53 (3H, s, Me), 6.02 (1H, dd, J 15.7 and 8.8Hz, 2'-H), 6.97 (1H, d, J 15.7Hz, 1'-H), 7.12 - 7.61 (4H, m, aromatic); i.r. (film) 1685 cm^{-1} (C=O); m/z 230 (5%), 174 (8), 159 (43); 145 (100), 132 (19), 129 (26), 128 (30), 115 (43).

g) 1-Acetyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene tosylhydrazone (24)

A solution of 1-acetyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene (3.0 g, 0.013 mole) in ethanol (2 ml) was warmed to 35°C and added to a

solution of p-toluenesulphenylhydrazide (2.67 g, 0.014 mole) in ethanol (19 ml) at 35°C, containing 5 drops of a 1% v/v solution of concentrated hydrochloric acid in ethanol. The mixture was left stirring under dry nitrogen for 70 h at room temperature and then placed in a freezer for 48 h. The white crystals were filtered off and recrystallised to give 1-acetyl-2-(E-3',4',4'-trimethylpent-1'-enyl)benzene tosylhydrazone (24) as a white solid (4.8 g, 94%), m.p. 121 - 122°C (from ethanol) (Found: C, 69.6; H, 7.8; N, 7.05. $C_{23}H_{30}N_2O_2S$ requires C, 69.3; H, 7.6; N, 7.0%); δ_H (80MHz; $CDCl_3$) 0.85 (9H, s), (3H, d, J 6.8Hz, 3'-H), 1.93 (1H, m, 3'-H), 2.09 (3H, s, Me C=N), 2.41 (3H, s, tosyl Me), 5.94 (1H, dd, J 15.7 and 8.2Hz, 2'-H), 6.30 (1H, d, J 15.7Hz, 1'-H), 7.01 - 7.98 (8H, m, aromatic), 8.15 (1H, brs, N-H).

6) Preparation of 1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene tosylhydrazone

A) Attempted preparation of tosylhydrazone (39)/(40) from 2-bromoacetophenone

a) 2-(2'-bromophenyl)-2-methyl-1,3-dioxolane

This was prepared by the method of Schiemenz and Kaack¹⁵⁸, by the addition of 2-bromoacetophenone (36.0 g, 0.18 mole) to a solution containing ethylene glycol (22.3 g, 0.36 mole), p-toluene sulphonic acid monohydrate (0.5 g) in dry toluene (100 ml). The mixture ^{was} heated to reflux for 20 h and the water (10 ml) removed by azeotropic distillation. The mixture was cooled, washed with 20% w/v aqueous sodium carbonate solution (50ml) and water (2 x 30 ml). The combined washes were extracted

with ether (2 x 25 ml), the organic layers combined, dried, and the solvent removed in vacuo to give a yellow oil (45.7 g). Distillation yielded 2-(2'-bromophenyl)-2-methyl-1,3-dioxolane as a colourless oil (40.8 g, 93%), b.p. 85 - 87°C at 0.7 mmHg (lit.¹⁵⁸, 141 - 142°C at 15 mmHg); δ_{H} (80MHz; CDCl_3) 1.78 (3H, s, Me), 3.86 (4H, m), 7.06 - 7.70 (4H, m, aromatic).

b) 2-(2'-methyl-1,3'-dioxalan-2'-yl)benzaldehyde

A Grignard reagent was prepared by the addition of 2-(2'-bromophenyl)-2-methyl-1,3-dioxolane (40.5 g, 0.17 mole) in THF (150 ml) to magnesium (4.23 g, 0.17 mole) with stirring and under nitrogen. The mixture was then heated to 50°C for 1 h, then cooled to 10°C. Dry DMF (24.3 g, 0.33 mole) in THF (100 ml) was added over 0.5 h with stirring. The mixture was stirred at room temperature of 1 h, then heated to 60°C for 1 h. The mixture was cooled and poured into 25% w/v aqueous ammonium chloride solution (300 ml). The organic phase separated and the aqueous phase extracted with DCM (3 x 200 ml). The combined organic layers were washed with water (100 ml), dried and the solvent removed in vacuo to give an orange oil (37 g). Distillation gave 2-(2'-methyl-1',3'-dioxalan-2'-yl)benzaldehyde as a colourless oil (25.0 g, 78%), b.p. 94 - 97°C at 0.5 mmHg (lit.¹⁶³, no value given), (Found m/z 192.0785. $\text{C}_{11}\text{H}_{12}\text{O}_3$ requires m/z 192.0786); δ_{H} (80MHz; CDCl_3) 1.78 (3H, s, Me), 3.65 - 4.13 (4H, m), 7.32 - 7.90 (4H, m, aromatic), 10.68 (1H, s, CHO); i.r. (film) 2770 (aldehyde CH), and 1685 cm^{-1} (C=O); m/z 192 (8%), 191 (8), 177 (18), 149 (100), 148 (44), 147 (96), 132 (12), 121 (8), 105 (32), 91 (28), 87 (96).

c) Diethyl phenacylphosphonate

This was prepared by the Michaelis-Arbusov method¹⁷⁸ by the addition of triethylphosphite (17.4 g, 0.10 mole) dropwise over 1.1 h to phenacyl bromide (20.0 g, (0.10 mole) at 140°C. The byproduct ethyl bromide, was collected by distillation during the addition. The mixture was then heated to 160°C for 2 h and allowed to cool to give an orange oil (27 g). Careful distillation yielded a colourless oil (21 g, 83%). G.l.c. (OV1 2.5%, 180°C) indicated 17% Perkov product. Blending a number of distillate fractions diethyl phenacylphosphonate of 95% purity was obtained, to give a colourless oil (15.4 g, 60%), b.p. 128 - 130°C at 0.3 mmHg (lit.¹⁷⁹, 181 - 182°C at 2 mmHg).

d) 2[2-(E-3'-oxo-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (30)

A solution of diethyl phenacylphosphonate 5.6 g, 0.022 mole) in THF (25 ml) was added with stirring to sodium hydride (0.88 g, 60% w/w dispersion in oil, 0.022 mole) in THF (10 ml) over 0.5 h and under dry nitrogen. The mixture was stirred for 0.75 h, then 2-(2'-methyl-1',3'-dioxalan-2'-yl)benzaldehyde (3.85 g, 0.02 mole) in THF (25 ml) was added in one portion. The mixture was stirred for 0.5 h at room temperature, then 3 h at reflux and left to stir overnight at room temperature. The solvent was removed in vacuo and the residue partitioned between DCM (50 ml) and water (50 ml). The organic phase was separated and the aqueous phase extracted with DCM (3 x 25 ml). The combined organic layers were washed with water (2 x 25 ml), dried and the solvent removed in vacuo to yield a yellow oil (7 g). The crude product was recrystallised from ethanol to give

2[2-(E-3'-oxo-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (30) as a pale yellow solid (5.0 g; 86%), m.p. 103.5 - 105.0°C (from ethanol) (Found: C, 77.4; H, 6.21. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.16%); δ_H (80MHz; $CDCl_3$) 1.68 (3H, s, Me), 3.87 (4H, m), 7.17 - 8.07 (10H, m, aromatic and 2'-H), 8.6 (1H, d, J 15.7Hz, 1'-H); i.r. (nujol) 1665 cm^{-1} (C=O).

e) 2[2-E-3'-hydroxy-3'-phenylprop-1-enyl]-2-methyl-1,3-dioxolane (31)

Sodium borohydride (0.52 g, 14 mmole) was added to a solution of 2[2-(E-3'-oxo-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (30) (1.76 g, 6 mmole) in THF (12 ml) and methanol (8 ml) at -20°C. The mixture was left to stir for 1.5 h, then the solvent was removed in vacuo and the residue partitioned between DCM (25 ml) and water 25 ml). The organic phase^{was} separated and the aqueous phase extracted with DCM (3 x 10 ml). The combined organic layers were washed with water (10 ml), dried and the solvent removed in vacuo to give 2-[2-(E-3'-hydroxy-3'-phenylprop-1-enyl)phenyl]-2-methyl-1,3-dioxolane (31) as a colourless oil (1.76 g, 99%) (Found m/z 296.1416. $C_{19}H_{20}O_3$ requires m/z 296.1412); δ_H (80MHz; $CDCl_3$) 1.67 (3H, s, Me) 2.14 (1H, brd, J 3.6Hz, OH), 3.80 (4H, m), 5.42 (1H, brq, J 6.8 and 3.6 Hz, 3-H), 6.15 (1H, dd, J 15.7 and 6.8 Hz), 7.13 - 7.60 (10H, m, aromatic); i.r. (film) 3350 cm^{-1} (OH); m/z 296 (15%), 281 (19), 251 (6), 206 (15), 178 (10), 147 (18), 129 (60), 105 (100).

f) 2-[2-(E-3'-methoxy-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (32)

This was prepared by a general method suggested by Stoochnoff and Benoition¹⁵⁹. Sodium hydride (90 mg, 3.75 mmole) was added in one portion to a solution of 2-[2-E-3'-hydroxy-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (31) (0.74 g, 2.5 mmole) and methyl iodide (1.0 g, 7.5 mmole) in THF (10 ml), under dry nitrogen. The reaction was stirred for 1 h and water (0.5 ml) added dropwise to hydrolyse the excess sodium hydride. The solvent was removed in vacuo and the residue partitioned between DCM (10 ml) and water (10 ml). The organic phase ^{was} separated and the aqueous phase extracted with DCM (3 x 5 ml). The combined organic layers were washed with water 2 x 5 ml) dried and the solvent removed in vacuo to give 2-[2-(E-3'-methoxy-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (32) as a pale cream oil (0.77 g, 98%), (Found m/z 310.1557. C₂₀H₂₂O₃ requires m/z 310.1568); δ_H (80MHz; CDCl₃), 1.68 (3H, s, Me), 3.42 (3H, s, OMe), 3.85 (4H, m), 4.84 (1H, d, J 7.6Hz, 3'-H), 6.05 (1H, dd, J 15.8 and 7.6Hz), 7.1 - 7.62 (10H, m, aromatic and 1'-H); m/z 310 (1%), 292 (40), 279 (6), 207 (12), 191 (9), 143 (38), 121 (41), 105 (100).

g) Attempted preparation of

1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (38)
from (32)

i) This was attempted by a general procedure described Huet et al¹⁶⁰. A 10% w/w aqueous oxalic acid solution (1.5 ml) was added to silica gel 60 (0.22 g, Merck, 70 - 230 mesh) in

DCM (2 ml). After the silica gel had adsorbed the aqueous layer, 2-[2-(E-3'-methoxy-3'-phenylprop-1'-enyl)phenyl]-2-methyl-1,3-dioxolane (32) (0.075 g, 0.24 mmole) in DCM (1 ml) was added with stirring. The reaction was monitored by t.l.c. After 2 h t.l.c. indicated a multi component mixture. Solid sodium hydrogen carbonate (0.2 g) was added and left to stir for 0.5 h. The solids were filtered and washed with DCM (5 ml). The solvent was removed in vacuo to give a yellow oil (0.12 g). Proton n.m.r. (60MHz) indicated absence of product MeC=O (~2.5 ppm) and i.r. no carbonyl peaks present.

ii) The above reaction was repeated substituting 15% v/v aqueous sulphuric acid solution (1 drop) for aqueous oxalic acid solution. T.l.c. after 1 h indicated a multicomponent mixture. The usual work up and an i.r. on the yellow oil (0.13 g) indicated absence of a carbonyl peak.

iii) Concentrated hydrochloric acid (1 drop) was added to (32) (46 mg, 0.15 mmole) in ethanol (1 ml). The mixture was stirred for 1 h, then saturated aqueous sodium hydrogen carbonate (10 drops) added. The usual work up gave a yellow oil (50 mg). Proton n.m.r. (60MHz) indicated absence of O-Me group and absence of product MeC=O.

iv) Pyridinium ¹⁶²p-toluenesulphonate (12 mg, 0.05 mmole) was added to (32) (31 mg, 0.1 mmole) in acetone:H₂O (95:5, 2 ml) and heated to reflux for 1 h. The mixture was cooled and the solvent removed in vacuo. DCM (10 ml) was added and the solution washed with saturated aqueous sodium hydrogen carbonate (3 ml), water (2 x 3 ml), dried and the solvent removed in vacuo to give a yellow oil (62 mg). T.l.c. indicated a multicomponent mixture.

Proton n.m.r. (60 MHz) indicated absence of O-Me group and presence of MeC=O (2.4 ppm); i.r. (film) 3450 (OH), and 1710 m^{-1} (C=O).

v) This procedure was used to deprotect 2-(2'-methyl-1'-3'-dioxalan-2'-yl)benzaldehyde by Sternson *et al*¹⁶³.

The compound (32) (46 mg, 0.15 mmole) was added to glacial acetic acid:H₂O (3:1, 2 ml) and stirred for 0.5 h at 40°C. DCM (5 ml) and water (1 ml) was added, the organic phase separated and the aqueous phase was extracted with DCM (2 x 2 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 x 5 ml), water (5 ml), dried and the solvent removed in vacuo to give a yellow oil (49 mg). T.l.c. indicated a multi component mixture. Proton n.m.r. (60MHz) indicated absence of OMe group and MeC=O present.

B) Preparation of tosylhydrazone (39)/(40) from 2-bromobenzaldehyde.

a) E-2-Bromochalcone (33)

A solution of diethyl phenacylphosphonate (15.4 g, 0.06 mole) in THF (30 ml) was added with stirring to sodium hydride (2.4 g, 60% w.w dispersion in oil, 0.06 mole) in THF (10 ml) over 0.5 h and under dry nitrogen. The mixture was stirred for 1 h at room temperature, then 2-bromobenzaldehyde (10.6 g, 0.057 mole) in THF (30 ml) was added over 0.1 h. The mixture was stirred for 1 h at room temperature, then heated to reflux for 3 h and left to stir overnight at room temperature. The solvent was removed in vacuo and the residue partitioned

between DCM (50 ml) and water (50 ml). The organic phase was separated and the aqueous phase extracted with DCM (3 x 30 ml). The combined organic layers were washed with water (2 x 30 ml), dried and the solvent removed in vacuo to yield a yellow oil (18 g). The crude product was recrystallised from hexane and by cooling the solution to -40°C to give E-2-bromochalcone (33) as a pale yellow solid (12.6 g, 77%), m.p. $46.5 - 47^{\circ}\text{C}$ (from hexane) (Found: C, 62.4; H, 3.70. $\text{C}_{15}\text{H}_{11}\text{BrO}$ requires C, 62.7; H, 3.86%); δ_{H} (80MHz; CDCl_3) 7.12 - 8.21 (11H, m, aromatic and alkenic H); i.r. (melt) 1665 cm^{-1} (C=O).

b) 1-Bromo-2-(E-3'-hydroxy-3'-phenylprop-1'-enyl)benzene (34)

Sodium borohydride (2.26 g, 0.06 mole) was added in four portions over 1 h to 2-bromochalcone (33) (8.6 g, 0.03 mole) in THF (50 ml) and methanol (25 ml) at -30°C . The mixture was stirred for 2 h at -30°C , then warmed to 0°C and water (5 ml) added. The solvent was removed in vacuo and the residue partitioned between DCM (100 ml) and water (100 ml). The usual work up gave a white solid (8.5 g). The crude product was recrystallised from hexane to give 1-bromo-2-(E-3'-hydroxy-3'-phenylprop-1'-enyl)benzene (34) as a white solid (8.0 g, 92%), m.p. $72.0 - 73.0^{\circ}\text{C}$ (from hexane) (Found: C, 62.1; H, 4.54. $\text{C}_{15}\text{H}_{13}\text{BrO}$ requires C, 62.3; H, 4.53%); δ_{H} (80MHz; CDCl_3) 2.22 (1H, brs, OH), 5.41 (1H, brd, J 6.3Hz, 3'-H), 6.30 (1H, dd, J 15.7 and 6.3Hz, 2'-H), 6.95 - 7.60 (10H, m, aromatic and 1'-H); i.r. (melt) 3360 cm^{-1} (OH).

c) 1-Bromo-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (35)

1-Bromo-2-(E-3'-^{hydroxy}~~methoxy~~-3'-phenylprop-1'-enyl)benzene (34) (7.2 g, 0.024 mole) in THF (70 ml) was added dropwise over 0.25 h

to a stirred suspension of sodium hydride (0.74 g, 0.03 mole) and methyl iodide (14.1 g, 0.1 mole) in THF (50 ml) at 0 - 5°C, under dry nitrogen. The mixture was stirred for 1.25 h at 5°C, then allowed to warm up to room temperature. Water (5 ml) was added dropwise and the solvent removed in vacuo. The usual work up gave a yellow oil (7.3 g). Distillation gave 1-bromo-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (35) as a colourless oil (6.9 g, 95%), b.p. 147 - 150°C at 0.1 mmHg (Found: 63.6; H, 5.11%; M^+ , 304.0228. $C_{16}H_{15}BrO$ requires C, 63.8; H, 4.98%; M, 304.0287); δ_H (80MHz; $CDCl_3$) 3.41 (3H, s, OMe), 4.85 (1H, d, J 6.9Hz, 3'-H), 6.21 (1H, dd, J 15.8 and 6.9Hz, 2'-H), 6.93 - 7.60 (10H, m, aromatic and 1'-H), i.r. (film) 1090 cm^{-1} (C-O); m/z 304 (4%), 302 (4), 237 (4%), 207 (19), 185 (20), 155 (11), 121 (54), 105 (100).

d) 2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzaldehyde (36)

This was prepared by the method described in experiment (5.d.) using 1-bromo-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (35) (3.46 g, 11 mmole). After work up, flash chromatography, eluting with petrol:ether (97:3 to 94:6), gave 2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzaldehyde (36) as a yellow oil (2.1 g, 7.6%), (Found m/z 252.1147. $C_{17}H_{16}O_2$ requires m/z 252.1157); δ_H (80MHz; $CDCl_3$) 3.41 (3H, s, OMe), 4.88 (1H, d, J 6.7Hz, 3'-H), 6.24 (1H, dd, J 15.8 and 6.7Hz, 2'-H), 7.16 - 7.85 (10H, m, aromatic and 1'-H), 10.29 (1H, s, CHO); i.r. (film) 2740 (aldehyde H), 1695 (C=O), and 1090 cm^{-1} (C-O); m/z 252 (3%), 207 (44), 189 (60), 131 (42), 121 (27), 115 (100), 105 (15).

e) 1-Hydroxyethyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene
(37)

This was prepared by the method described in experiment (5.e.) using 2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzaldehyde (36) (1.98 g, 7.88 mmole). The usual work up gave 1-hydroxyethyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (37) as a colourless oil (2.0 g, 97%), (Found m/z 268.1461. $C_{18}H_{20}O_2$ requires m/z 268.1463; δ_H (80MHz, $CDCl_3$) 1.45 (3H, d, J 6.4 and 1Hz, Me), 1.85 (1H, brs, OH), 3.38 (3H, s, OMe), 4.83 (1H, d, J 6.7Hz, 3'-H), 5.19 (1H, q, J 6.4Hz), 6.14 (1H, dd, J 15.8 and 6.7Hz, 2'-H), 6.98 (1H, d, J 15.8Hz, 1'-H), 7.15 - 7.65 (9H, m, aromatic); i.r. (film) 3420 cm^{-1} (OH); m/z 286 (1%), 250 (9), 236 (10), 221 (46), 207 (60), 189 (77), 121 (58), 115 (100), 105 (64).

f) 1-Acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (38)

This was prepared by the method described in experiment (5.f.) using 1-hydroxy-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (37) (1.1 g, 4.1 mmole). The usual work up and dry column flash chromatography, eluting with petrol:ether (88:12) gave 1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (38) as a colourless oil (0.65 g, 60%), (Found m/z 266.1300. $C_{18}H_{18}O_2$ requires m/z 266.1307); δ_H (80MHz; $CDCl_3$) 2.53 (3H, s, MeC=O), 3.40 (3H, s, OMe), 4.82 (1H, d, J 7.0Hz, 3'-H), 6.10 (1H, dd, J 15.8 and 7.0Hz, 2'-H), 7.15 (1H, d, J 15.8Hz, 1'-H), 7.21 - 7.68 (9H, m, aromatic; i.r. (film) 1685 cm^{-1} (C=O), and 1090 cm^{-1} (C-O).

g) 1-Acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene tosylhydrazone (39/(40))

A solution of 1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (38) (0.64 g, 2.4 mmole) in ethanol (1 ml) was warmed to 35°C and added to a solution of p-toluenesulphenylhydrazide (1.35 g, 7.2 mmole) in ethanol (20 ml) at 35°C. The mixture was stirred for 28 h under dry nitrogen at room temperature. T.l.c. indicated a mixture of E- and Z-tosylhydrazones. The solvent was removed in vacuo to give a yellow oil. Dry column flash chromatography eluting with petrol:ethylacetate (90:10 to 80:20) gave two solids. No solvent for recrystallisation was found.

a) 1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene tosylhydrazone (39) (98 mg, 9%), m.p. 79.5 - 81.0°C; i.r. 3215 cm⁻¹ (NH).

b) 1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene tosylhydrazone (40) (0.67 g, 64%), m.p. 88.0 - 90.0°C (Found: C, 68.8; H, 5.80; N, 6.65. C₂₅H₂₆N₂O₃S requires C, 69.1; H, 6.03; N, 6.45%); δ_H (200MHz; CDCl₃) 2.05 (3H, s, MeC=N), 2.39 (3H, s, tosyl Me), 3.34 (3H, s, OMe), 4.71 (1H, d, J 7.3Hz, 3'-H), 6.10 (1H, dd, J 15.7 and 7.3Hz, 2'-H), 6.73 (1H, d, J 15.7Hz, 1'-H), 7.07 - 7.45 (11H, m, aromatic), 7.90 (2H, d, J 8.3Hz, aromatic), 8.28 (1H, brs, NH); i.r. (nujol) 3220 cm⁻¹ (NH).

h) Attempted preparation of 1-acetyl-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (38) from (35)

i) This was attempted by a general procedure described by Gilman¹
A Grignard reagent was prepared by the addition of

1-bromo-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (35) (3.03 g, 10 mmole) in THF (6 ml) to magnesium (0.26 g, 11 mmole) with stirring and under dry nitrogen. The temperature was maintained below 10°C during the addition, left to stir at room temperature for 1 h, then cooled to 0°C.

Dry cadmium chloride (1.1 g, 6 mmole) was added in one portion with stirring at room temperature for 2 h. After 0.5 h the cadmium chloride dissolved. The mixture was cooled to -20°C and acetyl chloride (0.94 g, 0.012 mole) in THF (3 ml) was added in one portion, then left to stir overnight at room temperature. The usual work up gave a brown oil (2.5 g). G.l.c. (200°C) comparison of the oil with a pure sample of (38) indicated no product (38) in the oil present.

ii) A Grignard reagent was prepared by the addition of (35) (0.61 g, 2 mmole) in THF (8 ml) to magnesium (54 mg, 2.2 mmole) with stirring and under dry nitrogen as described in (5.d.).

The Grignard reagent was cooled to 0°C and dry N,N-dimethylacetamide (0.52 g, 6 mmole) in THF (5 ml) was added over 0.25 h, then left to stir overnight.

The usual work up gave a yellow oil (0.5 g). Proton n.m.r. (60MHz) indicated no product (38) present, only the product resulting from hydrolysis of the Grignard reagent.

i) 1-Hydroxy-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (32)
from (30)

The preparation of the Grignard reagent described in (5.d.) was repeated, then cooled to -10°C. Acetaldehyde (0.26 g, 6 mmole) in THF (5 ml) was added dropwise over 0.25 h,

then left to stir overnight at room temperature. The usual work up gave a brown oil (0.52 g). T.l.c. indicated 2 components.

Flash chromatography, eluting with petrol:ether (85:15) gave:

i) colourless oil (0.35 g). G.l.c. (200°C) indicated product was a mixture of (35) and the product resulting from hydrolysis of the Grignard reagent.

(ii) 1-Hydroxy-2-(E-3'-methoxy-3'-phenylprop-1'-enyl)benzene (37) (0.10 g, 18%) as a colourless oil.

7) Preparation of 1-acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazones

a) Diethyl methanephosphonate

This was prepared by the method of Coutrot, Snouss and Savignac¹⁸⁰ by the addition of diethylphosphite (69.05 g, 0.5 mole) in dry benzene (150 ml) to a solution of sodium ethoxide (12 g, 0.525 moles of sodium) in 'super dry' ethanol (350 ml) at room temperature. After 1 h of stirring, methyl iodide (74.5 g, 0.525 mole) in dry benzene (100 ml) was added and the reaction temperature kept below 35°C. After work up, distillation yielded diethyl methanephosphonate as a colourless oil (66.5 g, 69%), b.p. 78-81°C at 20 mmHg (lit.¹⁸¹, b.p. 51°C at 1 mmHg).

b) Diethyl (3,3-dimethylbutan-2-one)phosphonate

This was prepared by the method of Mathey and Savignac¹⁶⁶, by the addition of diethyl methanephosphonate (30.4 g, 0.2 mole) in the THF (80 ml) to butyllithium (147 ml, 1.5 M solution in hexane, 0.22 mole in THF (160 ml) at -60°C, under dry nitrogen. Dry solid copper (I) iodide (41.9 g, 0.22 mole) was added in one

portion and the reaction stirred vigorously for 0.25 h, then allowed to warm up to -30°C and left to stir for 1 h. The mixture was cooled to -45°C and freshly distilled and degassed trimethylacetyl chloride (25.3g, 0.21 mole) in THF (140 ml) was added dropwise. The mixture was stirred at -45°C for 3 h, then left stirring overnight. Water (200 ml) was added to the black suspension and the mixture stirred for 0.1 h. The mixture was filtered through a bed of celite and washed with DCM (400 ml). The procedure was repeated and the solids washed with DCM (200 ml). The aqueous phase was separated and extracted with DCM (2 x 100 ml). The combined organic layers were dried and the solvent removed in vacuo to yield a pale yellow oil (53 g). Distillation yielded diethyl (3,3-dimethylbutan-2-one)phosphonate as a colourless oil (40.5 g, 86%), b.p. $85-87^{\circ}\text{C}$ at 0.1 mmHg (lit.¹⁶⁶, b.p. $97-100^{\circ}\text{C}$ at 0.5 mmHg); δ_{H} (60MHz; CDCl_3) 1.08 (9H, s), 1.24 (6H, t, J 6Hz), 3.08 (2H, d, J 21Hz), 4.1 (4H, t, J 6Hz).

c) 1-Bromo-2'-(E-4',4'-dimethyl-3'-oxopent-1'-enyl)benzene (41)

A solution of diethyl(3,3-dimethylbutan-2-one)phosphonate (9.0 g, 0.038 mole) in THF (30 ml) was added with stirring to sodium hydride (0.96 g, 0.04 mole) in THF (20 ml) over 1 h, under dry nitrogen. The mixture was stirred for 1 h, then 2-bromobenzaldehyde (7.0 g, 0.038 mole) in THF (20 ml) was added over 0.1 h and then left to stir at room temperature overnight. The mixture was heated to reflux for 2 h, cooled and the solvent removed in vacuo. The residue^{was} partitioned between DCM (50 ml) and water (50 ml), the aqueous phase separated and extracted with DCM (3 x 25 ml). The combined organic layers were washed with

water (2 x 25 ml), dried and the solvent removed in vacuo to yield a yellow solid (10.3 g). The compound was recrystallised from petrol 60/80 to ^{give} 1-bromo-2-(E-4',4'-dimethyl-3'-oxopent-1'-enyl)benzene (41) as a pale yellow solid (9.0 g, 89%), m.p. 65.0-66.5°C (from hexane) (Found: C, 58.1; H, 5.65. $C_{13}H_{15}BrO$ requires C, 58.4; H, 5.66%); δ_H (80MHz; $CDCl_3$) 1.22 (9H, s), 7.05 (1H, d, J 15.5Hz, 2'-H), 7.15-7.68 (4H, m, aromatic), 8.00 (1H, d, J 15.5Hz, 1'-H); i.r. (nujol) 1675 cm^{-1} (C=O).

d) 1-Bromo-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene
(42)

Sodium borohydride (0.83 g, 0.022 mole) was added to a solution of 1-bromo-2-(E-4',4'-dimethyl-3'-oxopent-1'enyl)benzene (41) (6.0 g, 0.022 mole) in THF (30 ml) and methanol (15 ml) at -25°C.

T.l.c. (petrol:ether, 80:20) indicated reduction was complete after 0.5 h. Water (5 ml) was added and the mixture allowed to stir at 0°C for 0.5 h. The solvent was removed in vacuo and the residue partitioned between DCM (50 ml) and water (30 ml). The organic phase was separated and the aqueous phase extracted with DCM (3 x 10 ml). The combined organic layers were washed with a brine solution (10 ml), water (10 ml), dried and the solvent removed in vacuo to yield 1-bromo-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (42) as a colourless oil (5.98 g, 99%), (Found m/z 270.0439.

$C_{13}H_{17}BrO$ requires m/z 270.0443); δ_H (80 MHz; $CDCl_3$) 0.97 (9H, z), 1.68 (1H, d, J 3Hz, OH), 3.94 (1H, dd, J 7 and 3Hz, 3'-H), 6.18 (1H, dd, J 15.8 and 7Hz), 6.90 (1H, d, J 15.8Hz, 1'-H),

6.91-7.54 (4H, m, aromatic; i.r. (film) 3360 cm^{-1} (OH);
 m/z 270 (1%), 269 (2), 213 (13), 210 (100), 189 (41), 132 (78),
 115 (9), 103 (20).

A 3,5-dinitrobenzoate derivative was prepared and recrystallised from isopropanol, m.p. $48.5\text{--}50^{\circ}\text{C}$ (Found: C, 51.9; H, 4.16; N, 6.05. $\text{C}_{20}\text{H}_{19}\text{BrN}_2\text{O}_6$ requires C, 51.85; H, 4.13; N, 6.05%).

e) 1-Bromo-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene
(43)

This was prepared by a general method suggested by Stoochnoff and Benoiton¹⁵⁹. Sodium hydride (0.74 g, 0.031 mole) was added in three portions over 1.5 h, to a solution of 1-bromo-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (42) (6.9 g, 0.026 mole) and methyl iodide (10.9 g, 0.077 mole) in THF (90 ml), under dry nitrogen. The reaction was stirred overnight with waterbath cooling. Water (2 ml) was added carefully to hydrolyse excess sodium hydride and the solvent removed in vacuo. DCM (100 ml) and water (100 ml) was added, the organic phase separated and the aqueous phase extracted with DCM (2 x 40 ml). The combined organic layers were washed with water (2 x 50 ml), dried and the solvent removed in vacuo to give a yellow oil (7.3 g). The crude product was distilled to give 1-bromo-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (43) as a colourless oil 6.3 g, 87%), b.p. $90\text{--}92^{\circ}\text{C}$ at 0.1 mmHg (Found m/z 284.0608. $\text{C}_{14}\text{H}_{19}\text{BrO}$ requires m/z 284.0600); δ_{H} (80MHz; CDCl_3) 0.98 (9H, s), 3.38 (3H, s, OMe), 3.40 (1H, d, 3'-H), 6.08 (1H, dd, J 15.8 and 6.7Hz, 2'-H), 6.87 (1H, d, J 15.8Hz, 1'-H), 6.90 (4H, m, aromatic); i.r. (film) 1090 cm^{-1} (C-O); m/z 284 (8%),

282 (6), 267 (13), 227 (64), 171 (13), 146 (46), 131 (100), 115 (89), 103 (83).

f) 2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzaldehyde (44)

This was prepared by the method described in experiment (5.d.) using 1-bromo-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (43) (7.0, 25 mmole). After work up, the crude product (5.8 g) was distilled to give 2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzaldehyde (44) as a colourless oil (4.5 g, 78%), b.p. 111-118°C at 0.5 mmHg (Found m/z 232.1470. $C_{15}H_{20}O_2$ requires m/z 232.1463); δ_H (80MHz; $CDCl_3$) 0.94 (9H, s), 3.32 (3H, s, OMe), 3.34 (1H, d, J 7.9Hz, 3'-H), 6.01 (1H, dd, J 15.8 and 7.9Hz, 2'-H), 7.23-7.85 (5H, m, aromatic and 1'-H), 10.31 (1H, s, CHO); i.r. (film) 2740 (aldehyde C-H), 1695 (C=O), and 1090 cm^{-1} (C-O); m/z 232 (8%), 191 (26), 185 (8), 175 (100), 147 (50), 127 (51), 111 (98), 100 (28).

g) Hydroxyethyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (45)

This was prepared by the method described in experiment (5.e.) using 2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzaldehyde (44) (4.40 g, 0.019 mole). The usual work up gave 1-hydroxyethyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (45) as a colourless oil (4.6 g, 98%), (Found m/z 248.1775. $C_{16}H_{24}O_2$ requires m/z 248.1776); δ_H (80MHz; $CDCl_3$) 0.94 (9H, s), 1.46 (3H, d, J 6.5Hz, Me), 2.09 (1H, br s, OH), 3.30 (4H, m, OMe and 3'-H), 5.19 (1H, q, J 6.5Hz), 5.93 (1H, dd, J 15.8 and 8Hz, 2'H), 6.83 (1H, d, J 15.8 Hz, 1'-H), 7.20-7.58 (4H, m, aromatic); i.r. (film) 3380 cm^{-1} (OH); m/z 248 (15%),

230 (10), 227 (19), 191 (57), 159 (64), 131 (100), 115 (27), 103 (7), 91 (10).

h) 1-Acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene
(46)

This was prepared by the method described in experiment (5.f.) using 1-hydroxyethyl-2-(E-3-methoxy-4',4'-dimethylpent-1-enyl)benzene (45) (4.8 g, 0.019 mole). The ether solution after filtration was washed with water (2 x 100 ml) and to the combined aqueous washes, water was added (200 ml) and extracted with ether (3 x 100 ml). The ether layers were combined and the solvent removed in vacuo to give a brown oil (4.21 g). The crude product was distilled to yield 1-acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (46) as a colourless oil (3.7 g, 77%), b.p. 102-104°C at 0.05 mmHg (Found: C, 78.2; H, 9.10%; M⁺, 246.1618. C₁₆H₂₂O₂ requires C, 78.0; H, 9.00%; M, 246.1619); δ_{H} (80MHz; CDCl₃) 0.93 (9H, s), 2.55 (3H, s, Me C=O), 3.28 (1H, d, J 8.1Hz, 3'-H), 3.22 (3H, s, OMe), 5.94 (1H, dd, J 15.4 and 8.1Hz, 2'-H), 7.03 (1H, d, J 15.4Hz, 1'-H), 7.30-7.59 (4H, m, aromatic); i.r. (film) 1685 (C=O) and 1090 cm⁻¹ (C-O); m/z 246 (5%), 231 (24), 227 (20), 215 (39), 199 (71), 189 (67), 145 (75), 131 (45), 115 (100), 103 (55).

i) 1-Acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene
tosylhydrazone (47)/(48)

A solution of 1-acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (46) (0.98 g, 4 mmole) in ethanol (0.5 ml) was warmed to 35°C and added to a solution of p-toluenesulphonylhydrazide (0.9 g, 4.8 mmole) in ethanol (8 ml) at 35°C, containing 3 drops of a 1% v/v solution of concentrated

hydrochloric acid in ethanol. The mixture was left stirring for 48 h at room temperature. The solvent was removed in vacuo to give a white solid (1.9 g). Dry column flash chromatography, eluting with petrol:ethylacetate (85:15) gave two white solids, deduced to be the E- and Z-tosylhydrazones. No solvent for recrystallisation was found.

(i) 1-acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (47) (0.33 g, 20%), m.p. 78°C decomp. (Found: C, 66.7; H, 7.56; N, 6.40. $C_{23}H_{30}N_2O_3S$ requires C, 66.6; H, 7.29; N, 6.70%); δ_H (200MHz; $CDCl_3$) 0.87 (9H, s with 5Hz splitting), 2.14 (3H, s with 4Hz splitting), 2.44 (3H, s, tosyl Me), 3.08 (1H, m, 3'-H), 3.16 (s, OMe), 3.21 (s, OMe), 6.06 (1H, m, 2'-H), 6.83 (1H, m, 1'-H), 7.16-7.79 (9H, m, aromatic and NH); i.r. (nujol) 3220 cm^{-1} (NH).

(ii) 1-acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene (48) tosylhydrazone (1.0 g, 60%), m.p. 48-49.5°C (Found: C, 66.4; H, 7.29; N, 7.0. $C_{23}H_{30}N_2O_3S$ requires C, 66.6; H, 7.29; N, 6.70%); δ_H (80MHz; $CDCl_3$) 0.88 (9H, s), 2.09 (3H, s, Me C=N), 2.41 (3H, s, tosyl Me), 3.13 (1H, d, J 8.0Hz, 3'-H), 3.21 (3H, s, OMe), 5.93 (1H, dd, J 15.9 and 8.0Hz, 2'-H), 6.48 (1H, d, J 15.9Hz, 1'-H), 7.04-7.92 (9H, m, aromatic and NH); i.r. (nujol) 3320 cm^{-1} (NH).

8) Preparation of 1-acetyl-2-(E-3'-ethyl-4',4'-dimethyl-1'-enyl)benzene tosylhydrazone

a) 1-(Trimethylsiloxy)but-1-ene

This was prepared by the method of House, Czuba, Gall and Olmstead¹⁸² by the reaction of butanal (54 g, 0.75 mole) with

trimethylchlorosilane (98 g, 0.9 mole), and triethylamine (182 g, 1.8 mole) in dry DMF (300 cm³).

Distillation at atmospheric pressure gave 1-(trimethylsiloxy)but-1-ene as a colourless oil (61 g, 57%), b.p. 118-124°C (lit.¹⁸², 56-62°C at 75 mmHg).

b) 2-Ethyl-3,3-dimethylbutanal

This was prepared by the method of Reetz, Maier, Heimbad, Giannis and Anastassios¹⁶⁷ by the reaction of 1-(trimethylsiloxy)but-1-ene (57 g, 0.4 mole) and tert-butylchloride (111 g, 1.2 mole) in dry DCM (1.3 L), in the presence of anhydrous zinc chloride (9.5 g, 0.08 mole).

Distillation yielded 2-Ethyl-3,3-dimethylbutanal as a colourless oil (7.2 g, 14%), b.p. 130-140°C at 20-25 mmHg (lit.¹⁶⁷, 130°C at 14 mmHg); δ_H (60MHz; CDCl₃) 0.98 (9H, s), 1.01 (3H, t, Me), 1.5-2.3 (3H, m), 10.05 (1H, d); i.r. (film) 1720 cm⁻¹ (C=O).

c) 1-Bromo-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene
(49)

This was prepared by the method described in experiment (5.c.) using diethyl(2-bromobenzyl)phosphonate (19 g, 0.062 mole) and 2-ethyl-3,3-dimethylbutanal (7.2 g, 0.056 mole). After work up, chromatography gave 1-bromo-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene (49) as a colourless oil (10.2 g, 65%),

(Found m/z 282.0816. C₁₅H₂₁Br requires m/z 282.0807)

δ_H (200MHz; C₆D₆) 0.86 (9H, s), 0.87-1.70 (6H, m Et and 1'-H), 5.75 (1H, dd, J 15.6 and 9.9Hz, 2'-H), 6.64-7.46 (5H, m, aromatic); m/z 282 (16%), 280 (15), 223 (69), 145 (11), 144 (100), 129 (38), 115 (18).

d) 2-(E-3'-Ethyl-4',4'-dimethylpent-1'-enyl)benzaldehyde (50)

This was prepared by the method described in experiment (5.d.) using 1-bromo-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl) benzene (49) (9.75 g, 0.347 mole). Distillation gave 2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzaldehyde (50) as a pale yellow oil (7.52 g, 94%), b.p. 104-106°C at 0.01 mmHg (Found : C, 83.4; H, 9.60%; M^+ , 282.0816. $C_{16}H_{16}O$ requires C, 83.3; H, 9.5%; M , 282.0807); δ_H (80MHz; $CDCl_3$) 0.92 (9H, s), 0.86-2.14 (6H, m, Et and 3'-H), 5.88 (1H, dd, J 15.6 and 9.6Hz, 2'-H), 7.10 (1H, d, J 15.6Hz), 7.24-7.87 (4H, m, aromatic) 10.30 (1H, s, CHO); i.r. (film) 2740 (aldehyde H) and 1695 cm^{-1} (C=O); m/z 230 (16%), 174 (58), 146 (10), 145 (100), 131 (16), 119 (25), 100 (22), 77 (15).

e) 1-Hydroxyethyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl) benzene (51)

This was prepared by the method described in experiment (5.e.) using 2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl) benzaldehyde (50) (6.21 g, 0.027 mole). The usual work up gave 1-hydroxyethyl-2-(3'-ethyl-4',4'-dimethylpent-E-1'-enyl)benzene (51) as a pale yellow oil (6.4 g, 96%), (found m/z 246.1985. $C_{17}H_{26}O$ requires m/z 246.1983) δ_H (80MHz; $CDCl_3$) 0.93 (9H, s), 0.87-2.33 (7H, m), 1.49 (3H, d, J 6.4Hz, Me), 1.89 (1H, brs, OH), 5.21 (1H, q, J 6.4Hz), 5.80 (1H, dd, J 15.5 and 9.5Hz, 2'-H), 6.61 (1H, d, J 15.5Hz, 1'-H), 7.16-7.57 (4H, m, aromatic) i.r. (film 3340 cm^{-1} (OH).

A 3,5-dinitrobenzoate was prepared and recrystallised from isopropanol, m.p. 111-112.5°C (Found: C, 66.50; H, 6.44; N, 6.59. $C_{24}H_{28}N_2O_6$ requires (C, 66.44; H, 6.41; N, 6.36%).

f) 1-Acetyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene (52)

This was prepared by the method described in experiment (5.f.) using 1-hydroxyethyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene (51) (6.17 g, 0.025 mole). The usual work up and distillation gave 1-acetyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene (52) as a colourless oil (5.3 g, 86%), b.p. 108-111°C at 0.01 mmHg (Found: m/z 244.1821. $C_{17}H_{24}O$ requires m/z 244.1827); δ_H (80MHz; $CDCl_3$) 0.86-1.86 (6H, m), 0.91 (9H, s), 2.54 (3H, s, Me), 5.84 (1H, dd, J 15.6 and 9.5Hz, 2'-H), 6.75 (1H, d, J 15.6Hz, 1'-H), 7.20-7.62 (4H, m, aromatic); i.r. (film 1685 cm^{-1} (C=O); m/z 244 (12), 231 (80), 202 (8), 188 (26), 173 (33), 145 (100), 128 (18), 115 (20), 103 (12).

A 2,4-dinitrophenylhydrazone was prepared and recrystallised from ethanol, m.p. 180-181°C (Found: C, 64.9; H, 6.68; N, 13.30. $C_{23}H_{28}N_4O_4$ requires C, 65.0; H, 6.65; N, 13.2%).

g) 1-Acetyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (53)

A solution of 1-acetyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene (52) (2.94 g, 0.012 mole) in ethanol (2 ml) was warmed to 35°C and added to a solution of p-toluene sulphonylhydrazide (2.46 g, 0.013 mole) in ethanol (25 ml) at 35°C, containing 5 drops of a 1% v/v solution of concentrated hydrochloric acid in ethanol. The mixture was left stirring under dry nitrogen for 48 h at room temperature and then placed in a freezer for 24 h. The white crystals were filtered off and recrystallised from ethanol and petrol 60/80 to give

1-acetyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (53) as a white solid (4.0 g, 81%), m.p. 131.5-132.5°C (from ethanol) (Found: C, 69.6; H, 7.75; N, 6.8. $C_{24}H_{32}N_2O_2S$ requires C, 69.9; H, 7.8; N, 6.8%); δ_H (80MHz; $CDCl_3$) 0.76-1.67 (6H, m), 0.85 (9H, s), 2.08 (3H, s, MeC=N), 2.41 (3H, s, tosylMe), 5.73 (1H, dd, J 15.6 and 9.1Hz, 2'-H), 6.25 (1H, d, J 15.6Hz), 7.00-7.97 (9H, m, aromatic and NH); i.r. (nujol) 3210cm^{-1} (NH).

9) Preparation of 1-Bromo-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene tosylhydrazones

a) 1-Bromo-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (54)

This was prepared by a general method suggested by Corey¹⁶⁸. tert-Butyldimethylsilylchloride (15.4 g, 0.1 mole) was added to a solution of 1-bromo-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (42) (23 g, 0.085 mole) and imidazole (14.45 g, 0.21 mole) in dry DMF (50 ml), under dry nitrogen. The mixture was then stirred for 18 h at room temperature. The solvent was removed in vacuo and the residue partitioned between DCM (200 ml) and water (200 ml). The organic phase was separated and the aqueous phase extracted with DCM (2 x 50 ml). The combined organic layers were washed with 1% v/v aqueous hydrochloric acid solution (100 ml), saturated aqueous sodium hydrogen carbonate solution (100 ml), water (100 ml), dried and the solvent removed to yield 1-bromo-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (54) as a colourless oil (32.6 g, 100%), b.p. 110-113°C at 0.01 mmHg (Found: C, 59.2;

H, 8.16. $C_{19}H_{31}BrOSi$ requires C, 59.55; H, 8.15%); δ_H (80MHz; $CDCl_3$) 0.04 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.94 (18H, s), 3.89 (1H, d, J 7.2 and 1Hz, 3'-H), 5.09 (1H, dd, J 15.9 and 7.2Hz), 6.81 (1H, d, J 15.9Hz), 7.04-7.60 (4H, m, aromatic); m/z 327 (10%), 326 (15), 324 (15), 189 (7), 115 (15), 73 (26), 57 (100).

b) 2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzaldehyde (55)

A Grignard reagent was prepared by the addition of a solution of 1-bromo-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (54) (32 g, 0.083 mole) in THF (50 ml) to magnesium (2.22 g, 0.091 mole) with stirring and under dry nitrogen. The temperature was maintained between 15-20°C during the addition, then left to stir for 2 h at 30°C. The reaction was cooled to 10°C and dry DMF (18.2 g, 0.25 mole) in THF (110 ml) was added dropwise over 0.25 h, then left to stir overnight at room temperature. The reaction mixture was poured into 25% v/v aqueous ammonium chloride solution (250 ml), the organic phase separated and the aqueous phase extracted with DCM (3 x 100 ml). The combined organic layers were washed with water (2 x 50 ml) and dried. The solvent was removed in vacuo to yield an orange oil (28 g), which was distilled to give 2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzaldehyde (55) as a colourless oil (24.8 g, 90%), b.p. 146-148°C at 0.05 mmHg (Found: C, 72.6; H, 10.0. $C_{20}H_{32}O_2Si$ requires C, 72.2; H, 9.7%); δ_H (80MHz; $CDCl_3$) 0.03 (3H, s, Si-Me), 0.05 (3H, s, Si-Me), 0.92 (18H, s), 3.90 (1H, d, J 7.3 and 1Hz), 6.10 (1H, dd, J 15.8 and 7.3Hz, 2'-H), 7.15-7.85 (5H,

m, aromatic) 10.31 (1H, s, CHO); i.r. (film) 2740 (aldehyde C-H), and 1700 cm^{-1} (C=O); m/z 274 (6%), 273 (23), 201 (23), 142 (11), 129 (9), 73 (100).

c) 1-Hydroxyethyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (56)

This was prepared by the method described in experiment (5.e.) using 2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzaldehyde (55) (24.5 g, 0.074 mole). The usual work up gave 1-hydroxyethyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (56) as a pale brown oil (25.8 g, 100%). [Found: m/z (positive Xenon, F.A.B.; thioglycerol) M^+ , 348.2484. $C_{21}H_{36}O_2Si$ requires m/z 348.2484); δ_H (80MHz; $CDCl_3$) 0.03 (3H, s, Me), 0.05 (3H, s, Me), 0.91 (18H, s), 1.46 (3H, d, J 6.4Hz, Me), 1.69 (1H, brs, OH), 3.85 (1H, d, J 7.2 and 1Hz, 3'-H), 5.19 (1H, q, J 6.4Hz), 6.03 (1H, dd, J 15.7 and 7.2Hz, 2'-H), 6.76 (1H, d, J 15.7Hz, 1'-H), 7.18-7.49 (4H, m, aromatic); i.r. (film) 3360 cm^{-1} (OH); m/z 292 (19%), 291 (82), 161 (23), 131 (35), 115 (32), 75 (67).

d) 1-Acetyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (57)

This was prepared by the method described in experiment (5.f.) using 1-hydroxyethyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (54) (25.4 g, 0.073 mole). The usual work up and distillation yielded 1-acetyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (55) as a pale yellow oil (23.0 g, 91%), b.p. $122-124^\circ\text{C}$ at 0.1 mmHg [Found: m/z (positive Xenon, F.A.B.; thioglycerol) M^+ , 346.2328. $C_{21}H_{34}O_2Si$ requires m/z 346.2328); δ_H (80MHz; $CDCl_3$)

0.03 (3H, s, Si-Me), 0.05 (3H, s, Si-Me), 0.91 (18H, s), 2.55 (3H, s, Me C=O), 3.84 (1H, d, J 7.7Hz, 3'-H), 6.02 (1H, dd, J 15.8 and 7.7Hz, 2'-H), 6.91 (1H, d, 15.8Hz, 1'-H), 7.16-7.66 (4H, m, aromatic); i.r. (film) 1690 cm^{-1} (C=O); m/z 290 (26%), 289 (100), 221 (5), 203 (8), 145 (6), 129 (31), 115 (26), 75 (53).

e) 1-Acetyl-2-[E-3'-(tert butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene tosylhydrazones (58)/(59)

A solution of 1-acetyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene (0.69 g, 2 mmole) in ethanol (0.5 ml) was warmed to 35°C and added to a solution of p-toluenesulphonylhydrazide (0.43 g, 2.3 mmole) in ethanol (4.5 ml) at 35°C , containing one drop of a 1% v/v solution of concentrated hydrochloric acid in ethanol. The mixture was left stirring under dry nitrogen for 56 h at room temperature and then placed in a freezer for 24 h. T.l.c. indicated a mixture of E and Z-tosylhydrazones. The white crystals were filtered off and recrystallised from ethanol:petrol 40/60 (1:3) to give 1-acetyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene tosylhydrazones (58)/(59) as a white solid (0.74 g, 70%) m.p. 128°C decomp. (from ethanol/petrol) (Found: C, 65.1; H, 8.22; N, 5.62. $\text{C}_{28}\text{H}_{42}\text{N}_2\text{O}_3\text{SSi}$ requires C, 65.3; H, 8.22; N, 5.44%); δ_{H} (80MHz; CDCl_3)-4.00 (3H, s, Si-Me), -4.04 (3H, s, Si-Me), 0.84 (18H, s), 2.06 (3H, s, Me C=N), 2.41 (3H, s, tosylMe), 3.60 (1H, d, J 7.2Hz, 3'-H), 6.00 (1H, q, J 15.9 and 7.2Hz, 2'-H), 6.43 (1H, d, J 15.9Hz, 1'-H), 7.07-7.92, (9H, m, aromatic and NH); i.r. (nujol) 3190, and 3240 cm^{-1} (NH, E and Z-tosylhydrazones).

10) Preparation of E-1-(2'-acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate tosylhydrazones

a) E-1-(2'-Acetylphenyl)-4,4-dimethylpent-1'-en-3-yl benzoate (62)

This was prepared by a general method suggested by Vogel¹⁸³ Benzoyl chloride (1.48 g, 0.01 mole) was added to solution of 1-acetyl-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (60) (1.63 g, 7 mmole) in dry pyridine (8 ml) with stirring at room temperature, under dry nitrogen. Water (8 ml) was added and the mixture left to stir for 1 h. DCM (40 ml) was added and the aqueous layer separated and extracted with DCM (2 x 20 ml). The combined organic layers were washed with 1M aqueous hydrochloric acid solutions (3 x 20 ml), saturated aqueous sodium hydrogen carbonate solution (2 x 20 ml), water (20 ml), dried and the solvent removed in vacuo to give an orange oil (2.3 g). Dry column flash chromatography, eluting with petrol:ether (80:20), gave E-1-(2'-acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate (62) as a colourless oil (2.35 g, 100%), b.p. 180-182°C at 0.1 mmHg (Found: C, 78.5; H, 7.23%; m^+ , 336.1724. $C_{22}H_{24}O_3$ requires C, 78.5; H, 7.19%; M, 336.1725); δ_H (80MHz, $CDCl_3$) 1.08 (9H, s), 2.50 (3H, s), 5.39 (1H, d, J 7.2Hz, 3'-H), 6.08 (1H, dd, J 15.8 and 7.2Hz, 2'-H), 7.12 (1H, d, J 15.8Hz, 1'-H), 7.03-7.60 (6H, m, aromatic), 8.06 (2H, m, aromatic); i.r. (film) 1740 (ester C=O), and 1685 cm^{-1} (ketone C=O); m/z 336 (5%), 279 (18), 262 (15), 231 (17), 214 (40), 199 (25), 175 (38), 145 (60), 105 (100).

b) E-1-(2'-Acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate tosylhydrazone (63)/(64)

A solution of E-1-(2'-acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate (62) (2.0 g, 6 mmole) in ethanol (3 ml) was warmed to 35°C and added to a solution of p-toluene sulphenylhydrazide (1.27 g, 6.8 mmole) in ethanol (12 ml) at 35°C, containing two drops of 10% v/v solution of concentrated hydrochloric acid in ethanol. The mixture was left stirring for 18 h at room temperature, under dry nitrogen. T.l.c. indicated a mixture of E and Z-tosylhydrazones. The solvent was removed in vacuo to give a white solid (3.2g). Dry column flash chromatography, eluting with petrol:ethylacetate (90:10 to 85:15) gave E-1-(2'-acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate tosylhydrazone (63) as a white solid (0.26 g, 9%), m.p. 62.0-63.0°C (Found: C, 68.5; H, 6.38; N, 5.48. $C_{29}H_{32}N_2O_4S$ requires C, 69.0; H, 6.40; N, 5.55%); i.r. (nujol) 3320 (NH), and 1750 cm^{-1} (C=O).

E-1-(2'-acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate tosylhydrazone (64) as a white solid (2.5 g, 84%), m.p. 79.0-80.5°C (Found: C, 68.5; H, 6.3; N, 5.48. $C_{29}H_{32}N_2O_4S$ requires C, 69.0; H, 6.40; N, 5.55%); δ_H (80MHz; $CDCl_3$) 1.01 (9H, s), 1.97 (3H, s, Me C=N), 2.40 (3H, s, tosylMe), 5.22 (1H, d, J 7.2Hz, 3'-H), 6.03 (1H, dd, J 15.8 and 7.2Hz, 2'-H), 6.65 (1H, d, J 15.8Hz, 1'-H), 7.10-8.10 (14H, m, aromatic and NH); i.r. (nujol) 3320 (NH), and 1740 cm^{-1} (C=O).

11) Preparation of 1-acetyl-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone

a) 1-Acetyl-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (60)

Tetrabutyl ammonium fluoride¹⁶⁸ (53 ml, 1.0 M solution in THF, 0.053 mole) was added to a solution of 1-acetyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl)benzene (57) (11.1 g, 0.032 mole) in THF (30 ml) with stirring at room temperature, under dry nitrogen. The mixture was stirred for 40 h and then the solvent removed in vacuo. The residue was partitioned between DCM (200 ml) and water (200 ml), the organic phase separated and the aqueous phase extracted with DCM (3 x 50 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), water (100 ml) dried and the solvent removed in vacuo to yield a red oil (11.6 g). Dry column flash chromatography, eluting with petrol 40/60:ethyl acetate (88:12 to 80:20), gave a yellow oil (6.3 g). Distillation yielded 1-acetyl-2-[E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (60) as a colourless oil (5.95 g, 80%), b.p. 119-121°C at 0.1 mmHg (Found: C, 77.8; H, 8.66%; M⁺, 232.1459. C₁₅H₂₀O₂ requires C, 77.55; H, 8.68%; M, 232.1463); δ_{H} (80MHz; CDCl₃) 0.95 (9H, s), 2.09 (1H, s, OH), 2.53 (3H, s, Me C=O), 3.92 (1H, d, J 7.12 and 1Hz, 3'-H), 6.10 (1H, dd, J 15.8 and 7.12Hz, 2'-H), 7.00 (1H, d, J 15.8 and 1Hz, 1'-H), 7.12-7.66 (4H, m, aromatic); i.r. (film) 3540 (OH), and 1680cm⁻¹ (C=O); m/z 232 (1%), 191 (38), 175 (66), 145 (100), 131 (70), 115 (49), 103 (10).

b) 1-Acetyl-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (61)

A solution of 1-acetyl-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (60) (1.16 g, 5 mmole) in ethanol (2 ml) was warmed to 35°C and added to a solution of p-toluenesulphonylhydrazide (1.1 g, 6 mmole) in ethanol (10 ml) at 35°C, containing one drop of a 1% v/v solution of concentrated hydrochloric acid in ethanol. The mixture was left stirring under dry nitrogen for 18 h at room temperature. The solvent was removed in vacuo to give a yellow solid (2.3 g). Dry column flash chromatography, eluting with petrol:ethyl acetate (75:35 to 70:30) gave 1-acetyl-2-(E-3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (61) as a white solid (1.66 g, 83%, m.p. 62-63.5°C (Found: C, 66.0; H, 7.35; N, 6.50. $C_{22}H_{28}N_2O_3S$ requires C, 66.0; H, 7.10; N, 6.8%); δ_H (200MHz; $CDCl_3$) 0.95 (9H, s), 1.84 (1H, brs, OH), 2.12 (3H, s, Me C=N), 2.40 (3H, s, tosyl Me) 3.85 (1H, d, J 6.5Hz, 3'-H), 6.13 (1H, dd, J 15.7Hz and 6.5Hz, 2'-H), 6.73 (1H, d, J 15.7Hz, 1'-H), 7.13-7.47 (6H, m, aromatic), 7.83 (3H, m, aromatic and N-H); i.r. (nujol) 3540 (OH), and 3220 cm^{-1} (NH).

12) Preparation of 1"-acetyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene

a) 1,2:5,6-Di-O-isopropylidene-D-mannitol

This was prepared by the method of Eibl¹⁸⁴.

Anhydrous zinc chloride (70.4g) was dissolved in dry acetone (352 ml) and stirred for 1 h, under a calcium chloride guard tube. D-Mannitol (36.4 g, 0.2 mole) was added and the

mixture stirred for 3 h, then the unreacted D-mannitol (8.0 g) filtered off. The solution was poured into aqueous potassium carbonate solution (88 g in 88 ml of water) with vigorous stirring and left overnight in a fridge. The solids were filtered off and the aqueous layer extracted with chloroform (1 x 200 and 2 x 100 ml). The filtered solids were slurried with chloroform (200 ml) filtered and the procedure repeated twice more. The combined organic layers were washed with 5% w/v aqueous ammonia solution (250 ml), water (250 ml), dried and the solvent removed in vacuo. The crude product was recrystallised to give

1,2:5,6-Di-O-isopropylidene-D-mannitol as a white solid (13.4 g, 32% based on reacted mannitol) m.p. 120 - 121°C (lit., 120 - 121°C).

Isopropylidene-R-glyceraldehyde

This was prepared by the method of Eibl¹⁸⁴.

Distillation gave isopropylidene-R-glyceraldehyde as a colourless oil (2.1 g, 40%), b.p. 48.0 - 50.0°C at 15 mmHg (lit.¹⁸⁵, 50-51°C at 18 mmHg).

b) 1"-Bromo-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene (25)

A solution of lithium diisopropylamide was prepared by the addition of butyllithium (4.7 ml, 1.5 M solution in hexane, 7 mmole) to diisopropylamine (0.71 g, 7 mmole) in THF (1 ml) at 0°C, under dry nitrogen.

The lithium diisopropylamide solution was added dropwise over 0.5 h to diethyl(2-bromobenzyl)phosphonate (19) (2.15 g, 7 mmole) in THF (5 ml) with stirring at 0°C, under dry nitrogen.

Isopropylidene-R-glyceraldehyde (0.83 g, 6.4 mmole) in THF (3 ml) was added over 0.1 h at 10°C. The mixture was stirred for 1 h, then poured into 10% w/v aqueous ammonium chloride solution (20 ml). The organic phase separated and the aqueous phase extracted with DCM (3 x 20 ml). The combined organic layers were washed with water (5 ml) dried and the solvent removed in vacuo. Chromatography (alumina), eluting with petrol:ether (95:5) gave

i) 1"-bromo-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl] benzene as a colourless oil (1.1 g, 61%), (Found m/z 284.0239. $C_{13}H_{15}BrO_2$ requires m/z 284.0236); δ_H (80MHz, $CDCl_3$) 1.44 (3H, s, Me), 1.49 (3H, s, Me), 3.70 (1H, dd, J 8.1 and 7.6Hz, 5-H), 4.19 (1H, dd, J 8.11 and 6.2Hz, 5-H), 4.73 (1H, m, 4-H), 6.21 (1H, dd, J 15.7 and 7.2Hz, 2'-H), 7.03 (1H, d, J 15.7Hz, 1'-H), 7.06 - 7.60 (4H, m, aromatic); m/z 284 (11%), 282 (12), 225 (5), 203 (6), 181 (21), 145 (11), 128 (20), 115 (22).

ii) 1"-bromo-2"-[Z-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl] benzene a colourless oil (0.08 g, 4%); δ_H (200MHz; $CDCl_3$) 1.34 (3H, s, Me), 1.45 (3H, s, Me), 3.69 (1H, dd, J 8.2 and 6.1Hz) 4.67 (1H, m), 5.78 (1H, dd, J 11.4 and 9.1Hz), 6.73 (1H, d, J 11.4Hz), 7.15 - 7.60 (4H, m, aromatic).

A repeat reaction using isopropylidene-R-glyceraldehyde (0.95 g, 7.3 mmole) gave (25) as a colourless oil (0.95 g, 7.3 mmole).

c) 2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl] benzaldehyde (26)

This was prepared by the method described in experiment (1.d.) using 1"-bromo-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)

ethenyl]benzene (25) (1.1 g, 3.9 mmole). The usual workup gave 2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzaldehyde (26) as a yellow oil (0.88 g, 96%), (Found m/z 232.1098.

$C_{14}H_{16}O_3$ requires m/z 232.1099); δ_H (80MHz; $CDCl_3$) 1.42 (3H, s, Me), 1.46 (3H, s, Me), 3.69 (1H, dd, J 8.2 and 7.4Hz, 5-H), 4.19 (1H, dd, J 8.2 and 6.2Hz, 5-H), 4.74 (1H, m, 4'-H), 6.11 (1H, dd, J 15.7 and 7.2Hz, 2'-H), 7.24 - 7.85 (5H, m, aromatic and 1'-H), 10.26 (1H, s, CHO); i.r. (film) 2720 (aldehyde CH), and 1695 cm^{-1} (C=O); m/z 232 (<1%), 217 (3), 175 (3), 144 (10), 131 (100), 129 (33), 115 (33), 103 (10).

d) 1"-Hydroxyethyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene (27)

This was prepared by the method described in experiment (1.e.) using 2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzaldehyde (26) (0.85 g, 3.6 mmole). The usual workup gave 1"-hydroxyethyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene (27) as a yellow oil (0.91 g, 100%), (Found m/z 248.1407. $C_{15}H_{20}O_3$ requires 248.1412); δ_H (80MHz; $CDCl_3$) 1.40 - 1.48 (9H, m, 3 x Me), 2.04 (1H, brs, OH), 3.66 (1H, t, J 8.0Hz, 5-H), 4.14 (1H, dd, J 8.0 and 6.1Hz, 5-H), 4.66 (1H, m, 4-H), 5.15 (1H, brq, J 6.5Hz), 6.00 (1H, dd, J 15.7 and 7.2Hz, 2'-H), 7.00 (1H, J 15.7Hz, 1'-H), 7.16 - 7.60 (4H, m, aromatic); i.r. (film) 3430 cm^{-1} (OH); m/z 248 (10%), 233 (7), 190 (18), 173 (16), 159 (39), 145 (16), 133 (60), 115 (25).

e) 1"-Acetyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl] benzene (28)

This was prepared by the method described in experiment (1.f.) using 1"-hydroxy-2"-[E-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene (27) (0.91 g, 3.7 mmole). The usual workup, followed by chromatography (alumina), eluting with petrol:ether (95:5 to 90:10) gave 1"-acetyl-2"-[E-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene (28) as a yellow oil (0.49 g, 55%), (Found m/z 246.1247. $C_{15}H_{18}O_3$ requires m/z 246.1256); δ_H (80MHz; $CDCl_3$) 1.39 (3H, s, Me), 1.44 (3H, s, Me), 2.53 (3H, s, Me C=O), 3.66 (1H, dd, J 8.1 and 7.6Hz, 5-H), 4.15 (1H, dd, J 8.1 and 6.1Hz, 5-H), 4.67 (1H, m, 4-H), 6.04 (1H, dd, J 15.7 and 7.3Hz, 2'-H), 7.19 (1H, J 15.7Hz, 1'-H), 7.24 - 7.68 (4H, m, aromatic) i.r. (film) 1685 cm^{-1} (C=O); m/z 246 (<1%), 171 (9), 146 (15), 145 (100), 132 (10), 115 (15), 103 (6).

f) 1"-Acetyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl] benzene tosylhydrazone (29)

A solution of 1"-acetyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene (28) (0.173 g, 0.7 mmole) in ethanol (1 ml) was warmed to 40°C and added to a solution of *p*-toluenesulphonylhydrazide (0.195 g, 1.05 mmole) in ethanol (1 ml) at 40°C , under dry nitrogen. The mixture was left stirring at 40°C for 8 h, then left stirring overnight at room temperature. The white crystals were filtered off and washed with ethanol (1 ml) to give (1"-acetyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene tosylhydrazone (29) as a white solid (0.137 g, 47%), m.p. $141.5 - 142.5^\circ\text{C}$ (from ethanol) (Found:

C, 63.5; H, 6.15; N, 6.64. $C_{22}H_{26}N_2O_4S$ requires C, 63.7; H, 6.32; N, 6.76%); δ_H (200MHz; $CDCl_3$) 1.41 (3H, s, Me), 1.44 (3H, s, Me), 2.10 (3H, s, Me C=N), 2.42 (3H, s, Tosyl Me), 3.62 (1H, t, J 8.1Hz, 5-H), 4.11 (1H, dd, J 8.1 and 6.2Hz, 5-H), 4.55 (1H, m, 4-H), 6.00 (1H, dd, J 15.7 and 7.7 Hz, 6.77 (1H, J 15.7Hz, 1'-H), 7.11 - 7.50 (7H, m, aromatic and NH), 7.86 (2H, m, aromatic); i.r. (nujol) 3220 cm^{-1} (NH).

PREPARATION AND THE DECOMPOSITION OF THE SODIUM SALTS OF THE
P-TOLUENESULPHONYLHYDRAZONES TO GIVE 1H-2,3-BENZODIAZEPINES
PROCEDURE.

The tosylhydrazones were dried overnight under high vacuum, over phosphorus pentoxide. The sodium salts were then prepared by the addition of a freshly prepared solution of sodium ethoxide in 'super-dry' ethanol to the tosylhydrazone in a solution of dry 1,2-dimethoxyethane or 'super-dry' ethanol. The solution was then stirred in the dark for 0.5 h. The ethanol was evaporated using a rotary evaporator under anhydrous conditions, and with a water bath temperature below 40°C. The solid sodium salt was then solvent dried overnight under high vacuum, over phosphorus pentoxide.

Freshly distilled dry solvent was added and the reaction mixture heated to 80-90°C, with stirring, under dry nitrogen in the dark. During the decomposition, samples of the reaction mixture were withdrawn and shaken with water to hydrolyse any residual sodium salt, and extracted with DCM. The DCM layer was analysed for unreacted tosylhydrazone by t.l.c. or h.p.l.c. and the reaction continued until no tosylhydrazone remained. After cooling, the by-product sodium *p*-toluenesulphinate was removed by the following procedures:

- (a) Filtration of the reaction mixture through celite, followed by evaporation of the solvent to give the products.
- (b) Evaporation of the solvent in vacuo, then addition of DCM and water. Extraction of the aqueous layer with DCM, followed by drying and evaporation of the combined DCM extracts gave the

products.

The ratio of the diastereomers was determined by ^1H n.m.r. and h.p.l.c. on the crude reaction mixture prior to purification by chromatography. In the n.m.r. method, the ratio was calculated using the integral signals of the C-5 hydrogen found in the 6-7 ppm region.

The diazepines were then purified by chromatography and identified by n.m.r. spectroscopy (Appendix I) and X-ray crystallography (Appendix III).

In most cases, the relative configuration of one of each pair of diastereomers was determined by X-ray crystallography. In a few cases, for similar substituents, the diastereomers were identified by comparison of their ^1H n.m.r. spectra with those of known analogues. In the following results, the relative configurations are given for the R enantiomer of the C-1' group.

1) 1-Methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepines
(67)/(69)

A. Cyclisation in cyclohexane

a) Sodium ethoxide (3.90 ml, 0.233M solution in 'super-dry' ethanol, 0.91 mmole) was added to the E/Z-mixture of 1-acetyl-2-(3'-phenylbut-1'-enyl)benzene tosylhydrazone (9) (0.40 g, 0.95 mmole) in THF (2 ml).

After the usual drying procedure, dry cyclohexane (25 ml) was added and the mixture heated to reflux for 6 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give a brown oil (0.187 g). Chromatography by

m.p.l.c., eluting with petrol:ether (60:40) gave

i) Colourless oil (0.145 g) which was analysed by g.l.c. (200°C) showing three components (50:28:22%).

ii) 1-methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepine (67)/(69) as a yellow oil (0.114 g, 45%).

The diastereomer ratio (67:69) was found to be 54:56 [measured by ^1H n.m.r. (360MHz; CDCl_3)] or 53:47 [measured by h.p.l.c. (silica, hexane:ether, 95:5)]. See Appendix II diagram 1.

b) Sodium ethoxide (3.48 ml, 0.13M solution in 'super-dry' ethanol, 0.45 mmole) was added to 1-acetyl-2-(E-3'-phenylbut-1'-enyl)benzene tosylhydrazone (14) (0.20 g, 4.8 mmole) in super dry ethanol (5 ml). After the usual drying procedure, dry cyclohexane (12.5 ml) was added and the mixture heated to reflux for 7.5 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give a brown oil (0.148 g).

The diastereomer ratio (67:69) was found to be 55:45 [measured by ^1H n.m.r. (80MHz; CDCl_3)].

c) Sodium ethoxide (3.64 ml, 0.311M solution in 'super-dry' ethanol, 1.13 mmole) was added to tosylhydrazone (14) (0.50 g, 1.19 mmole) in 'super-dry' ethanol (5 ml). After the usual drying procedure, dry cyclohexane (32 ml) was added and the mixture heated to reflux for 7 h with h.p.l.c. monitoring (silica, hexane:ether, 95:5) of the products formation:

Time/mins	Ratio (67:69)
1	53:47
5	56:44
10	55:45
20	58:42
30	56:44
60	53:47
100	55:45
120	55:45
180	54:46
240	55:45
300	56:44
360	55:45
420	55:45

The white precipitate was removed by filtration and the solvent removed in vacuo to give a brown oil (0.40 g).

The diastereomer ratio (67:69) was found to be 54:46 [measured by ^1H n.m.r. (80MHz; CDCl_3)].

B. Cyclisation in 1,2-dimethoxyethane

Sodium ethoxide (3.48 ml, 0.130M solution in 'super-dry' ethanol, 0.45 mmole) was added to tosylhydrazone (14) (0.20g, 4.8 mmole) in 'super-dry' ethanol (5 ml). After the usual drying procedure, dry DME (12.5 ml) was added and the mixture heated to reflux for 6 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give a brown oil (0.21 g).

The diastereomer ratio (67:69) was found to be 56:44 [measured by ^1H n.m.r. (80MHz; CDCl_3)]

The product mixtures from cyclisations A.(b), (c), and B. were combined and subjected to m.p.l.c., eluting with petrol:ether (85:15), to give (67)/(69) (0.39 g, 70%).

Further chromatography by m.p.l.c., eluting with petrol:ether (97:3 to 95:5) gave pure samples of

i) 1-methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepine (67) as yellow crystals, m.p. 63.0-64.0°C (from hexane) (Found: C, 82.6; H, 7.03; N, 10.80%; M^+ , 262.2456. $\text{C}_{18}\text{H}_{18}\text{N}_2$ requires C, 82.4; H, 6.92; N, 10.68%, M, 262.2470); see Appendix I table 1 for spectral characteristics. A crystallographic structure determination on (67) gave the relative configuration of the two chiral centres as C-1'(R), C-1(R). See Appendix II, picture 1 for X-ray structure.

ii) 1-methyl-4-(1'-phenyl)-1H-2,3-benzodiazepine (69) as yellow crystals, m.p. 83.0-84.0°C (from hexane) (Found: C, 82.8; H, 6.99; N, 10.70%; M^+ , 262.2460. $\text{C}_{18}\text{H}_{18}\text{N}_2$ requires C, 82.4; H, 6.92; N, 10.68%; M, 262.1470); see Appendix I table 1 for spectral characteristics.

2) 4-(1'-phenylethyl)-1H-2,3-benzodiazepine (70)

a) Sodium ethoxide (5.40 ml, 0.13M solution in 'super-dry' ethanol, 0.70 mmole) was added to

2-(E-3'-phenylbut-1'-enyl)benzaldehyde tosylhydrazone (13)

(0.30g, 0.74 mmole) in 'super-dry' ethanol (5 ml). After the usual drying procedure, dry cyclohexane (12.5 ml) was added and the mixture heated to reflux for 1.25 h. The white precipitate

was removed by filtration and the solvent removed in vacuo to give a brown oil (0.24 g). Chromatography by m.p.l.c., eluting with petrol:ether (80:20) gave 4-(1'-phenylethyl)-1H-2,3-benzodiazepine (77) as a yellow oil (0.164 g, 89%), (Found: m/z 248.1311. $C_{17}H_{16}N_2$ requires m/z 248.1313); see Appendix I table 2 for spectral characteristics.

b) The reaction was repeated using tosylhydrazone (13) (1.0 g, 2.47 mmole). The usual work and chromatography gave 4-(1'-phenylethyl)-1H-2,3-benzodiazepine (77) as a yellow oil (0.52 g, 85%).

3) 1-Methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepines(72)/(73)

A. Cyclisation in cyclohexane

a) Sodium ethoxide (3.82 ml, 0.522M solution in 'super-dry' ethanol, 2 mmole) was added to 1-acetyl-2-(E-3',4',4'-trimethyl-1'-enyl)benzene tosylhydrazone (24) (0.80 g, 2 mmole) in 'super-dry' ethanol (5 ml). After the usual drying procedure, dry cyclohexane (50 ml) was added and the mixture heated to reflux for 3.6 h. The white precipitate was removed by filtration and the solvent removed in-vacuo to give a yellow oil (0.50 g).

The diastereomer ratio (72:73) was found to be 58:42 [measured by 1H n.m.r. (200MHz; C_6D_6) and by h.p.l.c. (silica, hexane:ether, 97.5:2.5)]. See Appendix II, diagram 2.

Chromatography by m.p.l.c., eluting with petrol:ether (97.5:2.5) gave

i) 1-methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepine

(72) as yellow crystals (0.225 g, 53%), m.p. 102.0–103.0°C (from hexane) (Found: C, 79.0; H, 9.04, N, 11.50%; M^+ , 242.1775. $C_{16}H_{22}N_2$ requires C, 79.3; H, 9.15; N, 11.55%; M , 242.1783); see Appendix I table 3 for spectral characteristics.

A crystallographic structure determination on (72) gave the relative configuration of the two chiral centres as (C-1'(R), C-1(R). See Appendix III, picture 2.

ii) 1-methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepine (73) as yellow crystals (0.154 g, 32%), m.p. 90.0–90.5°C (from hexane) (Found: C, 79.3; H, 9.14; N, 11.50%; M^+ 242.2786.

$C_{16}H_{22}N_2$ requires C, 79.3; H, 9.15; N, 11.55%; M , 242.1783); see Appendix I table 3 for spectral characteristics.

b) The above reaction was repeated using tosylhydrazone (24) (1.2g, 3 mmole) in dry cyclohexane (80 ml) with h.p.l.c. monitoring of the products formation:

Time/mins	Ratio (53:47)
1	53:47
5	56:44
10	55:45
20	58:42
30	58:42
40	58:42
60	57:43
80	58:42
100	58:42
120	57:43

The white precipitate was removed by filtration and the

solvent removed in vacuo to give a yellow oil (0.65 g).

The diastereomer ratio (72:73) was found to be 57:43 [measured by h.p.l.c. (silica, hexane:ether (97:3))].

Dry column flash chromatography, eluting with petrol:ether (90:10) gave the diasteromeric mixture of 1-methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepines (72)/(73) as a yellow solid (0.53 g, 73%).

B. Cyclisation in 1,2-dimethoxyethane

The above reaction was repeated in dry DME (80 ml). The usual workup gave a yellow solid (0.80 g).

The diastereomer ratio (72:73) was found to be 55:45 [measured by ^1H n.m.r. (200MHz; C_6D_6)] or 56:44 (measured by h.p.l.c.).

Dry column flash chromatography, eluting with petrol:ether (90:10) gave 1-methyl-4-(1',2',2'-methylpropyl)-1H-2,3-benzodiazepines (72)/(73) as a yellow solid (0.55 g, 76%).

C. Cyclisation in dimethylformamide

Sodium ethoxide (6.73 ml, 0.594M solution in 'super-dry' ethanol, 4 mmole) was added to tosylhydrazone (24) (1.59 g, 4 mmole in dry DME (3 ml)). After the usual drying procedure, dry DMF (90 ml) was added and the mixture was heated to 80–85°C for 3 h. The solvent was removed in vacuo and DCM (50 ml) and water (40 ml) added. The usual workup gave a brown oil (1.1 g).

The diastereomer ratio (72:73) was found to be 57:43 [measured by ^1H n.m.r. spectrum (200MHz; C_6D_6) and by h.p.l.c.].

Dry column flash chromatography, eluting with petrol:ether

(90:10) gave 1-methyl-4-(1',2',2-methylpropyl)1H-2,3-benzodiazepines (72)/(73) as a yellow solid (0.73 g, 76%).

4) 1-Methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepines (75)/(76)

a) Sodium ethoxide (3.84 ml, 0.16M solution in 'super-dry' ethanol, 6 mmole) was added to 1-acetyl-2-(E-3'-methoxy-3-phenylprop-1'-enyl)benzene tosylhydrazone (40) (0.26 g, 6 mmole) in 'super-dry' ethanol (10 ml). After the usual drying procedure, dry cyclohexane (15 ml) was added and the mixture heated to reflux for 5 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give a yellow oil (0.17 g).

The diastereomer ratio (75:76) was found to be 44:56 [measured by ^1H n.m.r. (200MHz; CDCl_3)]. See Appendix II, diagram 3.

Chromatography by m.p.l.c., eluting with petrol:ethyl acetate (95:5 to 93:7) gave

i) 1-methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepine (76) as yellow crystals (74 mg, 44%), m.p. 92.7-93.2°C (from ethanol) (Found: C, 77.4; H, 6.47; N, 10.0%; M^+ , 278.1429. $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}$ requires C, 77.7; H, 6.50; N, 10.1%; M , 278.1419); see Appendix I table 4 for spectral data.

A crystallographic structure determination on (76) gave the relative configuration of the two chiral centres as C-1'(R), C-1(S). See Appendix III, picture 3.

ii) 1-methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepines (75) as yellow crystals (62 mg, 37%),

m.p. 73.5–74.3°C (from hexane) (Found: C, 77.8; H, 6.52; N, 10.1%; M^+ , 278.1426. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.50; N, 10.1%; M , 278.1419); see Appendix I table 4 for spectral data.

b) The above reaction was repeated using tosylhydrazone (40) (0.5 g, 1.15 mmole) in dry cyclohexane (40 ml) with h.p.l.c. monitoring of the products formation. (Silica, hexane:ether, 92:8).

Time/mins	Ratio (75:76)
1	42:58
5	44:56
10	44:56
20	45:55
40	44:56
60	44:56
120	46:54
180	46:54
240	45:55
300	44:56

The white precipitate was removed by filtration and the solvent removed in vacuo to give a yellow oil (0.2 g).

Dry column flash chromatography, eluting with petrol:ethyl acetate (94:6 to 90:10) gave

i) benzodiazepine (76) as a yellow solid (52 mg, 16%);

ii) benzodiazepine (75) as a yellow solid (48 mg, 15%).

5) 1-Methyl-4-(1'-methoxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (78)/(79)

A. Cyclisation in cyclohexane

Sodium ethoxide (4.53 ml, 0.265M solution in 'super-dry' ethanol, 1.2 mmole) was added to 1-acetyl-2-(E-3'-methoxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (48) (0.50 g, 1.2 mmole) in 'super-dry' ethanol (10 ml). After the usual drying procedure, dry cyclohexane (30 ml) was added and the mixture was heated to reflux for 1.5 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give yellow solid (0.37 g).

The diastereomer ratio (78:79) was found to be 8:92 [measured by ^1H Hn.m.r. (200MHz; CDCl_3)] or 10:90 [measured by h.p.l.c. (silica, hexane:ether)]. See Appendix II, diagram 4.

Dry column flash chromatography, eluting with petrol:ether (90:10) gave 1-methyl-4-(1'-methoxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (78)/(79) as a yellow solid (0.23 g, 75%).

B. Cyclisation in 1,2-dimethoxyethane

The above reaction was repeated using tosylhydrazone (48) (1.0g, 2.4 mmole) in dry DME (60 ml) for 2 h.

The white precipitate was removed by filtration and the solvent removed in vacuo to give a yellow oil (0.82 g).

The diastereomer ratio (78:79) was found to be 10:90 [measured by ^1H n.m.r. (200MHz; CDCl_3)] or 13:87 (measured by h.p.l.c.).

Dry column flash chromatography, eluting with petrol:ether (90:10) gave 1-methyl-4-(1'-methoxy-2',2'-dimethylpropyl)-

1H-2,3-benzodiazepines (78)/(79) as a yellow solid (0.31 g, 52%).

C. Cyclisation in dimethylformamide

The above reaction was repeated using tosylhydrazone (48) (0.8 g, 1.93 mmole) in dry DMF (50 ml) for 2.5 h. The solvent was removed in vacuo and DCM (40 ml) and water (20 ml). The usual workup gave a yellow solid (0.59 g).

The diastereomer ratio (78:79) was found to be 16:84 [measured by ^1H n.m.r. (200MHz; CDCl_3) and by h.p.l.c.]

Chromatography by m.p.l.c., eluting with petrol:ether (95:50 to 93:7) gave

i) 1-methyl-4-(1'-methoxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (79) as yellow crystals (0.336 g, 67%), m.p. 107.5-108.5°C (from hexane) (Found: C, 74.6; H, 8.70; N, 10.8%; M^+ , 258.1729. $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$ requires C, 74.4; H, 8.58; N, 10.8%; M , 258.1732); see Appendix I table 5 for spectral data.

A crystallographic structure determination on (79) gave the relative configuration of the two chiral centres as C-1'(R), C-1(S). See Appendix III, picture 4.

ii) 1-methyl-4-(1'-methoxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (78) as yellow crystals (60 mg, 12%), m.p. 88.0-89.5°C (from hexane) (Found: C, 74.2; H, 8.25; N, 10.7%; M^+ , 258.1730. $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$ requires C, 74.4; H, 8.58; N, 10.8%; M , 258.1732); see Appendix I table 5 for spectral characteristics.

6) 1-Methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (81)/(82)

A. Cyclisation in cyclohexane

Sodium ethoxide (4.63 ml, 0.28M solution in 'super-dry' ethanol, 1.3 mmole) was added to 1-acetyl-2-(E-3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (53) (0.54 g, 1.3 mmole) in dry DME (8 ml). After the usual drying procedure, dry cyclohexane (35 ml) was added and the mixture was heated to reflux for 4.5 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give a yellow oil (0.49 g).

The diastereomer ratio (81:82) was found to be 65:35 [measured by h.p.l.c. (silica, hexane:ether, 97:3)].

Chromatography by m.p.l.c., eluting with petrol:ether (97:3) gave

i) 1-methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (81) as yellow crystals (0.14 g, 42%), m.p. 113.0-114.0°C (from hexane) (Found: C, 79.8; H, 9.75; N, 10.9%; M^+ , 256.1939; see Appendix I, table 6 for spectral data.

The ^1H n.m.r. spectra (200MHz; C_6D_6) of (81) was found to be similar to benzodiazepine (72). Therefore the relative configuration of the two chiral centres found in (81) was C-1'(R), C-1(R). An X-ray structure determination has since been carried out to confirm this. See Appendix III, picture 5.

ii) 1-methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (82) as yellow crystals (75 mg, 22%), m.p. 110.0-110.5°C (from hexane) (Found: C, 79.6; H, 9.59;

N, 10.9%; M^+ , 256.1933. $C_{17}H_{24}N$ requires C, 79.6; H, 9.45; N, 10.9%; M , 256.1938); see Appendix I table 6 for spectral data.

The above reaction was repeated using tosylhydrazone (53) (1.24 g, 3 mmole) in dry cyclohexane (75 ml) for 4 h. The usual workup gave a yellow solid (0.83 g).

The diastereomer ratio (81:82) was found to be 63:37 [measured by 1H n.m.r. (200MHz; C_6D_6)] or 62:38 (measured by h.p.l.c.). See Appendix II, diagram 5.

Dry column flash chromatography, eluting with petrol:ethyl acetate (90:10) gave 1-methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (81)/(82) as a yellow solid (0.67 g, 90%).

B. Cyclisation in 1,2-dimethoxyethane

The above reaction was repeated in dry DME (75 ml) for 2 h. The solvent was removed in vacuo and DCM (50 ml) and water (50 ml) added. The usual work up gave a yellow solid (0.85g).

The diastereomer ratio (81:82) was found to be 62:38 [measured by 1H n.m.r. (200MHz; C_6D_6)] or 61:39 (measured by h.p.l.c.).

Dry column flash chromatography, eluting with petrol:ethyl acetate (95:5) gave a 1-methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (81)/(82) as a yellow solid (0.64g, 84%).

C. Cyclisation in dimethylformamide

The above reaction was repeated in dry DMF (75ml) for 2 h. The usual work up gave a yellow oil (0.85g).

The diastereomer ratio (81:82) was found to be 61:39 [measured by ^1H n.m.r. (200MHz; C_6D_6)] or 60:40 (measured by h.p.l.c.).

Chromatography gave 1-methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1,2,3-benzodiazepines (81)/(82) as a yellow solid (0.66g, 86%).

8) 1-Methyl-4-[1'(tert-butyldimethylsilyloxy)-2',2'-dimethylpropyl]-1H-2,3-benzodiazepines (84)/(85)

A. Cyclisation in cyclohexane

Sodium ethoxide (1.40 ml, 0.586M solution in 'super-dry' ethanol, 0.82 mole) was added to 1-acetyl-2-[E-3'-(tert-butyldimethylsilyloxy)-4',4'-dimethylpent-1'-enyl]benzene tosylhydrazones (58)/(59) (0.42g, 0.82 mole) in dry DME (1 ml). After the usual drying procedure, dry cyclohexane (21 ml) was added and the mixture heated to reflux for 2 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give yellow oil (0.29g).

The diastereomer ratio (84:85) was found to be 9:91 [measured by n.m.r. (360MHz; CDCl_3)] or 10:90 [measured by h.p.l.c. (silica, hexane:ether, 96:4)]. See Appendix II, diagram 6.

Dry column flash chromatography, eluting with petrol:ether (96:4) gave 1-methyl-4-[1'-(tert-butyldimethylsilyloxy)-2',2'-dimethylpropyl]-1H-2,3-benzodiazepines (84)/(85) as a yellow

solid (0.27g, 92%). Further chromatography, eluting with petrol:ether (98:2 to 96:4) gave pure samples of

i) benzodiazepine (84) as yellow crystals, m.p. 70.7–71.2°C (from hexane) (Found: C, 70.0; H, 9.66; N, 7.22. $C_{21}H_{34}N_2OSi$ requires C, 70.3; H, 9.55; N, 7.81%); see Appendix I table 7 for spectral characteristics.

ii) benzodiazepine (85) as yellow crystals, m.p. 98.0–98.8°C (from methanol) (Found: C, 70.5; H, 9.65; N, 7.69. $C_{21}H_{34}N_2OSi$ requires C, 70.3; H, 9.55; N, 7.81%); see Appendix I table 7 for spectral characteristics.

The 1H n.m.r. spectra (360MHz; $CDCl_3$) of (85) was found to be similar to benzodiazepine (79). Therefore, the relative configuration of the two chiral centres assigned in (85) was C-1'(R), C-1(S).

B. Cyclisation in 1,2-dimethoxyethane

The above reaction was repeated using tosylhydrazones (58)/(59) (0.8g, 1.55 mmole) in dry DME (30 ml) for 2 h. The solvent was removed in vacuo and DCM (50 ml) and water (50 ml). The usual work up gave a yellow solid (0.65g).

The diastereomer ratio (84:85) was found to be 11:89 [measured by 1H n.m.r. (200MHz; $CDCl_3$)].

Dry column flash chromatography, eluting with petrol:ether (96:4) gave 1-methyl-4-(1'-(tert-butyldimethylsilyloxy)-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (84:85) as a yellow solid (0.41g, 75%).

C. Cyclisation in dry dimethylformamide

The above reaction was repeated in dry DMF (30 ml) for

2 h. The usual work up gave a yellow oil (0.7g).

The diastereomer ratio (84:85) was found to be 12:88 [measured by ^1H n.m.r. (200MHz; CDCl_3)].

Dry column flash chromatography, eluting with petrol:ether (96:4) gave 1-methyl-4-(1'-(tert-butyldimethylsilyloxy)-2',2'-dimethylpropyl]-1H-2,3-benzodiazepines (84:85) as a yellow solid (0.52g, 93%).

D. Preparation of benzodiazepine (84) from 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (90)
tert-Butyldimethylsilylchloride (0.16g, 1mmole) was added to a solution of 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (90) (0.214g, 0.88 mmole) and imidazole (60mg, 0.88 mmole) in dry DMF (0.5 ml), under dry nitrogen. The mixture was then stirred for 48 h at room temperature. The solvent was removed in vacuo and the residue partitioned between DCM (10 ml) and water 810 ml). The organic phase was separated and the aqueous phase extracted with DCM (2 x 10 ml). The combined organic layers were washed with 1M aqueous hydrochloric acid solution (2 x 10 ml), saturated aqueous sodium hydrogen carbonate solution (10 ml), water (10 ml), dried and the solvent removed in vacuo to give a yellow oil (0.24g). Dry column flash chromatography, eluting with petrol:ether (90:10) gave
 i) 1-methyl-4-(1'-(tert-butyldimethylsilyloxy)-2',2'-dimethylpropyl]-1H-2,3-benzodiazepine (84) as a yellow solid (0.14g, 45%), m.p. 70.5-71.5°C (from methanol); ^1H n.m.r. (200MHz, CDCl_3) was identical to benzodiazepine (12) made by

the cyclisation preparation. See Appendix II, diagram 7.

ii) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (90) (20mg), 10% recovery), m.p. 105.0 - 106.0°C (from hexane).

9) 1-Methyl-4-(2',2'-dimethylpropyl-1'-yl benzoate)1H-2,3-benzodiazepines (87)/(88)

Sodium ethoxide (3.95 ml, 0.38 M solution in 'super-dry' ethanol, 1.5 mmole) was added to E-1-(2'-acetylphenyl)-4,4-dimethylpent-1-en-3-yl benzoate tosylhydrazone (64) (0.88g, 1.5 mmole) in 'super-dry' ethanol (2 ml). After the usual drying procedure, dry cyclohexane (30 ml) was added and the mixture heated to reflux for 1 h. The white precipitate was removed by filtration and the solvent removed in-vacuo to give a yellow oil (0.53 g).

The diastereomer ratio (87:88) was found to be 41:59 [measured by ^1H n.m.r. (200MHz; CDCl_3)]. See Appendix II, diagram 8.

Dry column flash chromatography, eluting with petrol:ether (93:7 to 90:10) gave

i) 1-Methyl-4-(2',2'-dimethylpropyl-1'-yl benzoate)1H-2,3-benzodiazepines (87) as yellow crystals (0.189g, 36%), m.p. 165.0 - 166.0°C (from ethanol) (Found: C, 75.5; H, 7.1; N, 8.0. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$ requires C, 75.8; H, 6.9; N, 8.0%); see Appendix I table 8 for spectral characteristics.

A crystallographic structure determination on (87) gave the relative configuration of the two chiral centres as C-1'(R), C-1(R). See Appendix III, picture 6.

ii) 1-Methyl-4-(2',2'-dimethylpropyl-1'-yl benzoate)1H-2,3-benzodiazepines (88) as yellow crystals (0.284g, 54%), m.p. 119. - 119.5°C (from hexane) (Found: C, 75.9; H, 7.0; N, 8.1. $C_{22}H_{24}N_2O_2$ requires C, 75.8; H, 6.9; N, 8.0%); see Appendix I table 8 for spectral characteristics.

10) 1-Methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (90)/(91)

The preparations below used a different procedure to make lithium salts of 1-acetyl-2-(E-hydroxy-4',4'-dimethylpent-1'-enyl)benzene tosylhydrazone (61).

Butyllithium was added to a solution of the tosylhydrazone (61) in dry DME, then the mixture was heated to reflux. The usual work up and chromatography gave the benzodiazepines (90)/(91).

A. Addition of 1 molar equivalent of butyllithium to tosylhydrazone (61)

a) Butyllithium (0.72 ml, 1.40 M solution in hexane, 1 mmole) was added dropwise over 10 mins to tosylhydrazone (61) (0.40g, 1 mmole) in dry DME (20 ml) at -40°C, under dry nitrogen. The reaction mixture was allowed to reach room temperature, then heated to reflux. The formation of the products was monitored by h.p.l.c. [porous graphitic carbon (pgc), acetonitrile:THF, 90:10].

Time/mins	Ratio (90:91)
15	29:71
30	28:72
50	28.5:71:5
80	28:72
120	28:72
135	28:72

The solvent was removed in vacuo and DCM (10 ml) and 10% w/v aqueous ammonium chloride solution (10 ml) added. The usual work up gave a brown oil (0.32 g).

The diastereomer ratio (90:91) was found to be 29:71 [measured by ^1H n.m.r. (200MHz; CDCl_3)]. See Appendix II, diagram 9. Dry column flash chromatography, eluting with petrol:ether (75:25) gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl-1H-2,3-benzodiazepines (92)/(93) as a yellow oil (0.196g, 80%); δ_{H} (200MHz; CDCl_3) 0.88 (s, tert-Bu), 0.91 (s, tert-Bu), 2.15 (1H, br s, OH), 2.30 (3H, m, 1-Me) 2.72 (1H, q, J 6.6Hz, 1-H), 4.31 [br s, 1'-H, benzodiazepine (92)], 4.97 (s, 1'-H, benzodiazepine (93)], 6.65 (s, 5-H, benzodiazepine (92)], 6.93 [s, 5-H, benzodiazepine (93)] 7.32 - 7.66 (4H, m, aromatic).

The ^1H n.m.r. spectra of (91) was found to be identical with the ^1H n.m.r. spectra of the product from the desilylated benzodiazepine (85) prepared in (10.D). Therefore the relative configuration of the two chiral centres found in (91) is C-'(R), C-1(S).

B. Addition of 1.95 molar equivalent of butyllithium to tosylhydrazone (61)

Butyllithium (1.37 ml, 1.42 M solution in hexane, 1.95 mmole) was added dropwise over 10 mins to tosylhydrazone (61) (0.40g, 1 mmole) in dry DME (25 ml) at -40°C , under dry nitrogen. The reaction mixture was allowed to reach room temperature, then heated to reflux. The formation of the products was monitored by h.p.l.c. (pgc, acetonitrile:THF, 90:10).

Time/mins	Ratio (90:91)
15	76:24
30	83:17
45	82:18
60	81:19
90	82:18
120	84:16
150	83.5:16.5
180	83.5:16.5
210	83.5:16.5
270	85:15
300	85:15
After workup	84:16

The solvent was removed in-vacuo and DCM (10 ml) and 10% w/v aqueous ammonium chloride solution (10 ml). The usual work up gave a brown oil (0.30g).

The diastereomer ratio (90:91) was found to be 86:14 [measured by ^1H n.m.r. (200MHz; CDCl_3)]. See Appendix II, diagram 10.

Dry column flash chromatography, eluting with petrol:ether (75:25) gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (90)/(91) as a yellow oil (0.17g, 70%).

C. Addition of 2.2 molar equivalent of butyllithium to tosylhydrazone (61)

a) Butyllithium (1.52 ml, 1.45 M solution in hexane, 2.2 mmole) was added dropwise over 10 mins to tosylhydrazone (61) (0.40g, 1 mmole) in dry DME (25 ml) at 0°C, under dry nitrogen. The reaction mixture was allowed to reach room temperature, then heated to reflux for 4 h.

The solvent was removed in vacuo and DCM (25 ml) and 10% w/v aqueous ammonium chloride solution (25 ml). The usual work up gave a brown oil (0.31g).

The diastereomer ratio (90:91) was found to be 97.3 [measured by ^1H n.m.r. (200MHz; CDCl_3)].

Dry column flash chromatography, eluting with petrol:ether (80:20) gave a yellow solid (0.177g, 72%). Recrystallisation from hexane gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (90) as a yellow solid (0.13g, 53%), m.p. 105.0 - 106.0°C (from hexane) (Found: C, 73.5; H, 8.30; N, 11.5%); see Appendix I table 9 for spectral characteristics.

Benzodiazepine (90) was converted to benzodiazepine (84) as described in preparation (8.D). The ^1H n.m.r. spectra was identical to that of benzodiazepine (84) made by a cyclisation reaction. Therefore the relative configuration of the two chiral centres found in (90) is C-1'(R), C-1(R).

b) Butyllithium (1.14 ml, 1.42 M solution in hexane,

1.65 mmole) was added dropwise over 10 mins to tosylhydrazone (61) (0.30g, 0.75 mmole) in dry DME (20 ml) at -40°C , under dry nitrogen. The reaction mixture was allowed to reach room temperature, then heated to reflux.

The formation of the products was monitored by h.p.l.c. (pgc, acetonitrile : 1,4-dioxan, 97.5:2.5).

Time/mins	Ratio (90:91)	% of total products (92:90:91)
15	81:19	1.5:80.0:18.5
30	82:18	1.0:81.5:17.5
60	84:16	1.0:83.0:16.0
90	85:15	2.0:83.0:15.0
135	87:13	3.0:85.0:12.0
180	86:14	4.0:83.0:13.0
240	86:14	6.0:81.0:13.0
300	87:13	9.0:79.0:12.0
360	88:12	7.0:82.0:11.0

The solvent was removed in vacuo and DCM (20 ml) and 10% w/v aqueous ammonium chloride solution (20 ml). The usual work up gave a brown oil (0.23g).

The diastereomer ratio (90:91) was found to be 90:10 [measured by ^1H n.m.r. (200MHz; CDCl_3)].

Dry column flash chromatography, eluting with petrol:ether (80:20) gave

i) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1 $\underline{\text{H}}$ -2,3-benzodiazepines (90)/(91) as a yellow oil (0.13g, 71%)

ii) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-5 $\underline{\text{H}}$ -2,3-benzodiazepine (92) as white crystals (12 mg, 7%), m.p. 134.5°C (from hexane) (Found: C, 73.9; H, 8.51; N, 11.5. $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}$)

requires C, 73.7; H, 8.25; N, 11.4%); δ_H (200MHz; $CDCl_3$) 1.02 (s, tert-Bu), 1.06 (s, tert-Bu), [ratio 1:2.6], 2.50 (s, 1-Me), 2.53 (s, 1-Me), [ratio 1:2.4], 2.84 (d, J_{AB} 12.3Hz, 5- H_B), 3.04 (d, J_{AB} 12.7Hz, 5- H_B) [ratio 1:2.4], 3.35 (d, J_{AB} 12.7Hz, 5- H_A), 3.74 (d, J_{AB} 12.3Hz, 5- H_A), [ratio 2.4:1], 3.92 (s, 2'-H), 3.94 (s, 2'-H), [ratio 2.6:1], 7.16-7.54 (4H, m, aromatic); i.r. (nujol) $3300cm^{-1}$ (OH); m/z 244 (4%), 229 (5), 188 (88), 172 (100), 159 (85), 144 (10), 130 (19), 116 (22), 89 (14).

D. 1-Methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (91)

Tetrabutylammonium fluoride (1.75 ml, 1.0 M solution in THF, 1.75 mmole) was added to a solution of 1-methyl-4-[1'-(tert-butyldimethylsilyloxy)-2',2'-dimethylpropyl]-1H-2,3-benzodiazepine (85) (0.25g, 0.7 mmole) in THF (0.75 ml) with stirring at 0°C, under dry nitrogen. The mixture was left to stir at room temperature for 2 h. The usual work up and chromatography, eluting with petrol ether (75:25) gave a yellow solid. Recrystallisation from hexane gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (91) as a yellow solid (0.12g, 70%), m.p. 110.5 - 115.5°C (from hexane (Found: C, 73.5; H, 8.20; N, 11.5%; M^+ , 244.1575. $C_{15}H_{20}N_2O$ requires C, 73.7; H, 8.25; N, 11.5%; M, 244.1575); see Appendix I table 9 for spectral characteristics.

11) Miscellaneous reactions involving benzodiazepines
(91)/(92)

A. Addition of excess butyllithium to a mixture of
tosylhydrazone (61) and benzodiazepine (91)

Butyllithium (0.87 ml, 1.45 M solution in hexane, 1.26 mmole) was added dropwise over 10 mins to tosylhydrazone (61) (0.18g, 0.45 mole) in dry DME (11 ml) at 0°C, under dry nitrogen. The mixture was heated to 60°C, then 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (91) (62 mg, 0.25 mmole) in dry DME (2 ml) was added in one portion. The mixture was then heated to reflux for 5 h. The usual work up gave a brown oil (0.20g).

The diastereomer ratio (90:91) was found to be 100:0 [¹H n.m.r. (200MHz; CDCl₃)]. Expected ratio (90:91) was 54:46.

Dry column flash chromatography, eluting with petrol:ether 75:25 to 40:60) gave

i) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (90) as a yellow solid (65 mg,* 38%) m.p. 105.0 - 106.0°C.

ii) tosylhydrazone (61) as a brown oil (35 mg).

iii) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-5H-2,3-benzodiazepine (92) as a white solid (36 mg,* 21%), m.p. 134.0 - 135.5°C.

* Yields based on theoretical yield plus added benzodiazepine (91).

B. Addition of 1 molar equivalent of butyllithium to benzodiazepine (91)

Butyllithium (0.26 ml, 1.42 M solution in hexane, 0.37 mmole) was added dropwise to 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (91) (90 mg, 0.37 mmole) and diphenyl ether (225 mg) in dry DME (10 ml) at 0°C, under dry nitrogen.

The mixture was then heated to reflux and the reaction monitored by h.p.l.c. (pgc, acetonitrile).

Time(t)/mins	Ratio of benzodiazepines (92:90:91)	*
0	0:2:98	100
15	49:1:50	76
30	66:2:32	72
60	81:2:17	70
90	85:2:13	67
120	89:2: 9	65
180	91:2: 6	64
240	94:2: 4	64

* - % of original total benzodiazepine area

$$= \frac{(x) \text{ at } t_n \times 100}{(x) \text{ at } t_o}$$

$$(x) = \frac{\text{total area of benzodiazepines}}{\text{area of diphenyl ether}}$$

The usual work up and chromatography, eluting with petrol:ether (80:20 to 50:50) gave

i) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines (90)/(91) as a yellow oil (5 mg, 6%).

ii) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-5H-2,3-benzodiazepine (92) as a white solid (60 mg, 66%),

m.p. 134 - 136°C.

C. Attempted preparation of benzodiazepines (90)/(91) via the standard procedure in cyclohexane

Sodium ethoxide (19.6 ml, 0.20 M solution in 'super-dry' ethanol, 4 mmole) was added to tosylhydrazone (61) (0.80g, 2 mmole) in 'super-dry' ethanol (5 ml). After the usual drying procedures, dry cyclohexane (40 ml) was added and the mixture heated to reflux for 6h with t.l.c. monitoring of the products formation. After 2 h, only a trace of benzodiazepines (90)/(91) was observed. After 4 h a precipitate was formed and the appearance of benzodiazepine (92). After 6 h approximately only 50% of the tosylhydrazone (61) had been consumed, a trace of benzodiazepine (90)/(91) and approximately 30% of benzodiazepine (92) had formed. No work up was attempted.

12) 1-Methyl-4-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-1H-2,3-benzodiazepines (93)/(94)

Sodium ethoxide (0.93 ml, 0.594 M solution in 'super-dry' ethanol, 0.55 mmole) was added to 1"-acetyl-2"-[E-2'-(2,2-dimethyl-1,3-dioxolan-4-yl)ethenyl]benzene tosylhydrazone (29) (0.229g, 0.55 mmole) in dry DME (1 ml). After the usual drying procedure, dry cyclohexane (14 ml) was added and the mixture heated to reflux for 5.5 h. The white precipitate was removed by filtration and the solvent removed in vacuo to give a yellow oil (0.146g).

The diastereomer ratio (93:94) was found to be 34:66 [measured by ^1H n.m.r. (200MHz; C_6D_6)] or 36:64 [measured by h.p.l.c. (silica, hexane:ether, 90:10)].

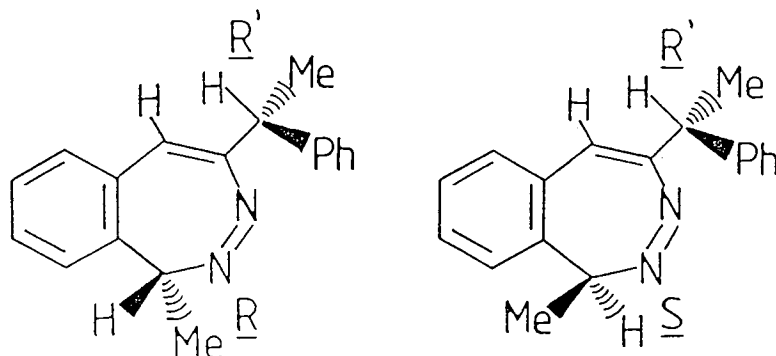
The yellow oil decomposed before separation of the diastereomers could be attempted.

The spectral data gave evidence for 1-methyl-4-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-1H-2,3-benzodiazepines (93)/(94) (Found: m/z 258.1366. $C_{15}H_{18}N_2O_3$ requires m/z 258.1368).

δ_H (200MHz; C_6D_6) 1.40 (3H, s, 2'-Me), 1.50 (3H, s, 2'-Me), 2.07 (3H, m, 1-Me), 2.66 (1H, m, 1-H), 4.12 (1H, d, J 6.8Hz, 5'-H), 4.40 (1H, m, 4'-H), 4.87 (t, J 6.7Hz, 5'-H), 5.25 (t, J 6.7Hz, 5'-H), 6.65 (s, 5-H), 6.84 (s, 5-H), 7.00 - 7.26 (4H, m, aromatic); m/z 258 (13%), 243 (6), 233 (2), 230 (2), 173 (9), 172 (8), 159 (18), 141 (31) 130 (87), 115 (35), 101 (100).

Appendix 1

Table 1

1-Methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepine

Product: Major (67)

Minor (69)

¹H N.m.r. spectral data

	(200MHz; CDCl ₃)	(200MHz; CDCl ₃)
1'-Me	1.73 (3H,d,J7.2Hz)	1.73 (3H,d,J7.2Hz)
1-Me	2.26 (3H,d,J6.6Hz)	2.23 (3H,d,J6.6Hz)
1-H	2.69 (1H,q,J6.6Hz)	2.72 (1H,q,J6.6Hz)
1'-H	4.40 (1H,q,J7.2Hz)	4.47 (1H,q,J7.2Hz)
5-H	6.32 (1H,s)	6.61 (1H,s)
Aromatic	7.23-7.57 (9H,m)	7.21-7.59 (9H,m)

¹³C N.m.r. spectral data

(50MHz; CDCl ₃)	(50MHz; CDCl ₃)
16.1 (1-Me), 20.7 (1'-Me),	16.0 (1-Me), 20.0 (1'-Me)
45.0 (C-1'), 71.0 (C-1),	44.3 (C-1'), 70.9 (C-1),
114.6 (C-5), 158.8 (C-4),	113.8 (C-5), 157.9 (C-4),
123.8, 126.7, 127.0, 129.1	123.8, 126.5, 127.8, 129.0
(tert.), 130.4, 133.2	(tert.), 130.4, 133.2
(tert.), 143.5 (tert.).	(tert.), 144.3 (tert.).

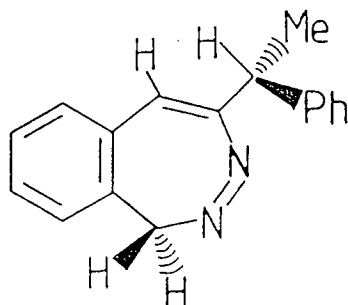
Mass spectral data

262 (17%), 233 (15), 219 (18),
 218 (68), 203 (38), 141 (12),
 128 (42), 115 (20), 105 (100),
 91 (21).

262 (15%), 233 (12), 219
 (20), 218 (72), 203 (34),
 141 (10), 128 (38),
 115 (100), 91 (21).

Appendix 1

Table 2

4-(1'-phenylethyl)-1H-2,3-benzodiazepine

(70)

¹H N.m.r. spectral data(200MHz; CDCl₃)

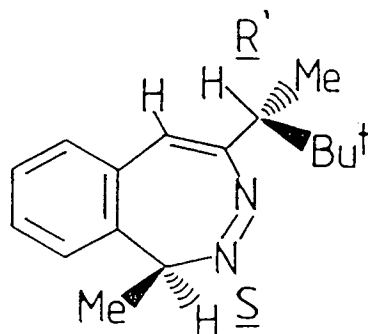
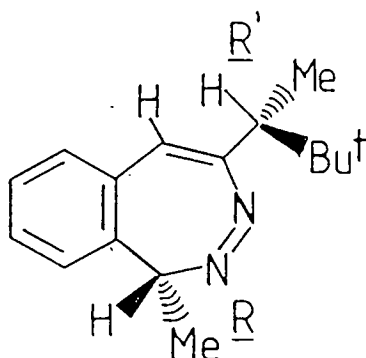
1'-Me	1.69 (d, J3.2Hz) and 1.78 (d, J3.2Hz)
1'-H	4.45 (1H, m)
quasi axial H	2.85 (1H, d, J9.0Hz)
quasi equatorial H	6.25 (1H, d, J9.0Hz)
5-H	6.34 (s) and 6.61 (s)
Aromatic	7.21-7.58 (9H, m)

¹³C N.m.r. spectral data(50MHz; CDCl₃)

20.0 and 20.6 (1'-Me),
 44.9 and 44.2 (C-1'), 70.9 and 71.0 (C-1),
 113.7 and 114.5 (C-5), 158.8 and
 157.8 (C-4), 123.8, 126.7, 127.0,
 129.1 (tert.), 130.4, 133.2 (tert.),
 143.5 (tert.).

Appendix 1

Table 3

1-Methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepine

Product: Major (72)

Minor (73)

 ^1H N.m.r. spectral data

	(200MHz; C_6D_6)	(200MHz; CDCl_3)
<u>tert</u> -Butyl	0.85 (9H, s)	0.97 (9H, s)
1'-Me	1.71 (3H, d, J7.2Hz)	1.34 (3H, d, J7.2Hz)
1-Me	2.12 (3H, d, J6.6Hz)	2.30 (3H, d, J6.6Hz)
1'-H	2.34 (1H, q, J7.2Hz)	3.05 (1H, q, J7.2Hz)
1-H	2.70 (1H, q, J6.6Hz)	2.77 (1H, q, J6.6Hz)
5-H	6.18 (1H, s)	6.30 (1H, s)
Aromatic	7.08-7.30 (4H, m)	7.60-7.37 (4H, m)

 ^{13}C N.m.r. spectral data

(50MHz; C_6D_6)	(50MHz; CDCl_3)
16.3 (1'-Me), 17.0 (1-Me), 28.4 (Bu^t -Me's), 33.7 (C-2'), 52.4 (C-1'), 71.7 (C-1), 116.0 (C-5), 157.8 (C-4), 124.0, 127.5, 128.0, 129.6, 130.4 (tert.), 133.9 (tert.).	15.0 (1'-Me), 16.0 (1-Me), 27.9 (Bu^t -Me's), 33.9 (C-2'), 48.3 (C-1'), 70.7 (C-1), 114.9 (C-5), 157.4 (C-4), 123.7, 126.9, 127.8, 129.0, 130.3 (tert.), 133.1 (tert.).

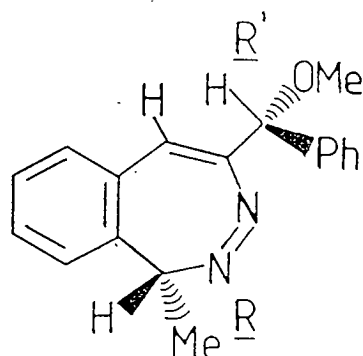
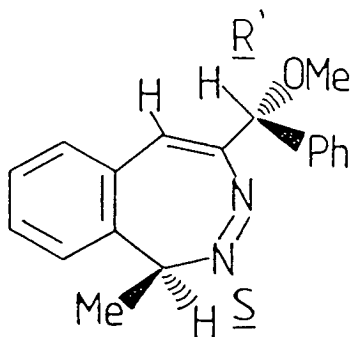
Mass spectral data

242 (<1%), 227 (8), 214 (4),
199 (5), 171 (4), 158 (47),
157 (100), 156 (9), 144 (8),
143 (38), 129 (65), 115 (35),
57 (60).

242 (<1%), 227 (3), 214
(2), 199 (3), 157 (100),
142 (30), 129 (37), 115
(21), 57 (27).

Appendix 1

Table 4

1-Methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepine

Product: Major (76)

Minor (75)

¹H N.m.r. spectral data

	(200MHz; CDCl ₃)	(200MHz; CDCl ₃)
1-Me	2.18 (3H,d,J6.6Hz)	2.31 (3H,d,J6.6Hz)
1-H	2.58 (1H,q,J6.6Hz)	2.86 (1H,q,J6.6Hz)
OMe	3.56 (3H,s)	3.35 (3H,s)
1'-H	5.70 (1H,s)	5.61 (1H,s)
5-H	6.70 (1H,s)	6.37 (1H,s)
Aromatic	7.22-7.65 (4H,m)	7.31-7.60 (4H,m)

¹³C N.m.r. spectral data

(50MHz; CDCl ₃)	(50MHz; CDCl ₃)
16.1 (1-Me), 56.9 (OMe),	16.1 (1-Me), 57.3 (OMe),
71.0 (C-1), 83.0 (C-1'),	71.1 (C-1), 84.2 (C-1'),
114.0 (C-5), 153.6 (C-4),	116.4 (C-5), 154.3 (C-4),
123.9, 126.9, 127.2,	123.9, 127.0, 127.5,
127.9, 128.0, 128.4,	128.1, 128.5,
129.1 (tert.), 131.1,	129.5 (tert.), 131.0,
132.9 (tert.),	132.7 (tert.),
139.8 (tert.).	139.1 (tert.).

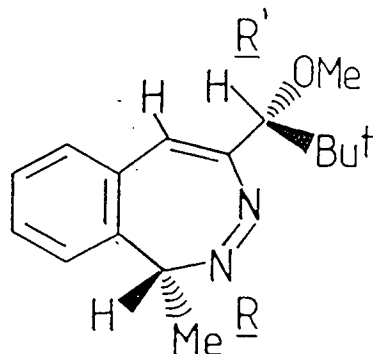
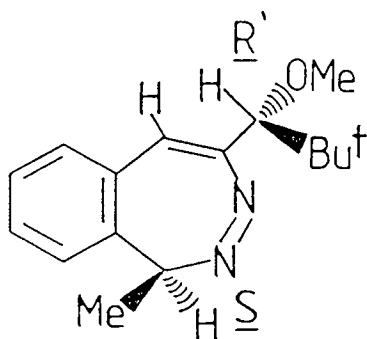
Mass spectral data

278 (2%), 250 (3), 235 (7),	278 (<1%), 219 (3), 121
219 (18), 204 (8), 131 (8),	(13), 87 (10), 85 (66),
128 (8), 121 (100), 115 (8),	83 (100).
105(18).	

Appendix 1

Table 5

1-Methyl-4-(1'-methoxy-2',2'-trimethylpropyl)-
1H-2,3-benzodiazepine



Product: Major (79)

Minor (78)

¹H N.m.r. spectral data

	(200MHz; CDCl ₃)	(200MHz; CDCl ₃)
<u>tert</u> -Butyl	0.85 (9H,s)	1.00 (9H,s)
1-Me	2.31 (3H,d,J6.6Hz)	2.33 (3H,d,J6.6Hz)
1-H	2.73 (1H,q,J6.6Hz)	2.78 (1H,q,J6.6Hz)
OMe	3.58 (3H,s)	3.51 (3H,s)
1'-H	4.41 (1H,s)	3.73 (1H,s)
5-H	6.75 (1H,s)	6.64 (1H,s)
Aromatic	7.36-7.70 (4H,m)	7.64-7.25 (4H,m)

¹³C N.m.r. spectral data

(50MHz; CDCl ₃)	(50MHz; CDCl ₃)
16.1 (1-Me), 26.6 (Bu ^t -Me's), 35.9 (C-2'), 57.6 (OMe), 71.3 (C-1), 91.5 (C-1'), 117.7 (C-5), 151.1 (C-4), 124.0, 127.1, 128.1, 129.3 (tert.), 130.1, 133.1 (tert.).	16.0 (1-Me), 25.6 (Bu ^t -Me's), 35.6 (C-2'), 57.4 (OMe), 71.3 (C-1), 88.7 (C-1'), 115.7 (C-5), 151.3 (C-4), 123.7, 127.0, 128.2, 129.0 (tert.), 130.1, 132.8 (tert.).

Mass spectral data

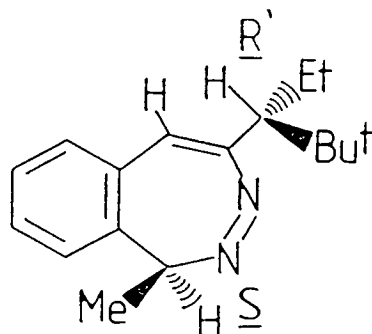
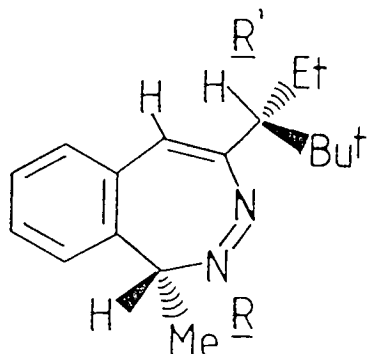
258 (3%), 231 (3), 187 (3),
 174 (12), 173 (100), 158 (22),
 141 (13), 127 (21), 115 (19),
 101 (74).

258 (2%), 231 (2), 187
 (3), 174 (14), 173 (100),
 158 (19), 141 (12), 115
 (19), 101 (61).

Appendix 1

Table 6

1-Methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-
1H-2,3-benzodiazepine



Product: Major (81)

Minor (82)

¹H N.m.r. spectral data

	(200MHz; CDCl ₃)	(200MHz; CDCl ₃)
Me	0.95 (3H,t,J7.3Hz)	1.11 (3H,t,J7.0Hz)
<u>tert</u> -Butyl	1.01 (9H,s)	0.87 (9H,s)
Methylene-H's	1.59 (1H,m), 1.86 (1H,m)	1.90 (1H,m), 2.16 (1H,m)
1-Me	2.30 (3H,d,J6.6Hz)	2.82 (3H,d,J6.6Hz)
1'-H	2.57 (1H,dd,J12 & 3Hz)	2.80 (1H,m)
1-H	2.83 (1H,q,J6.6Hz)	2.82 (1H,q,J6.6Hz)
5-H	6.41 (1H,s)	6.44 (1H,s)
Aromatic	7.32-7.64 (4H,m)	7.34-7.60 (4H,m)

¹³C N.m.r. spectral data

(50MHz; CDCl ₃)	(50MHz; CDCl ₃)
12.8 (C-2"), 16.1 (1-Me),	13.0 (C-2"), 16.0 (1-Me),
20.8 (C-1"), 28.3	21.6 (C-1"), 28.5
(Bu ^t -Me's), 34.2 (C-2'),	(Bu ^t -Me's), 33.5 (C-2')
57.4 (C-1'), 70.5 (C-1),	60.5 (C-1'), 70.9 (C-1),
116.4 (C-5), 154.3 (C-4),	117.8 (C-5), 154.4 (C-4),
123.7, 126.9, 127.7, 129.0,	123.6, 126.8, 127.8, 129.1
(tert), 130.3, 133.4 (tert).	(tert), 130.3, 133.3 (tert)

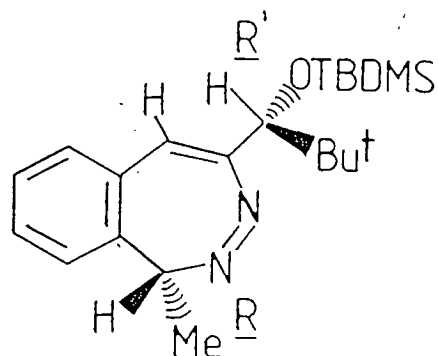
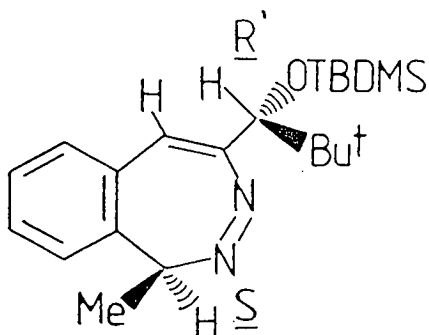
Mass spectral data

256 (1%), 241 (7), 228 (6),	256 (2%), 241 (13), 228 (10),
213 (7), 199 (8), 172 (43),	213 (10), 199 (12), 172 (54),
171 (100), 157 (48), 143 (90),	171 (100), 157 (55), 143 (90),
129 (97), 115 (60), 91 (20).	129 (90), 115 (70), 91 (35).

Appendix 1

Table 7

1-Methyl-4-[1'-(tert-butyl dimethylsilyloxy)-2',2'-
dimethylpropyl]-1H-2,3-benzodiazepine



Product: Major (85)

Minor (84)

¹H N.m.r. spectral data

(200MHz; CDCl₃)

(200MHz; CDCl₃)

Si-Me 0.09 (3H,s), 0.02 (3H,s) -0.08 (3H,s), 0.12 (3H,s)

tert-Butyl 0.82 (9H, s)

0.98 (9H, s)

Si-tert-Butyl 1.04 (9H, s)

1.09 (9H, s)

1-Me 2.29 (3H, d, J6.6Hz)

2.34 (3H, d, J6.6Hz)

1-H 2.70 (1H, q, J6.6Hz)

2.81 (1H, q, J6.6Hz)

1'-H 4.93 (1H, s)

4.29 (1H, s)

5-H 6.90 (1H, s)

6.70 (1H, s)

Aromatic 7.37-7.70 (4H, m)

7.37-7.62 (4H, m)

^{13}C N.m.r. spectral data

(50MHz; CDCl₃)

(50MHz; CDCl₃)

-5.3 (Si-Me), -4.6 (Si-Me),

-5.2 (Si-Me), -4.4 (Si-Me),

16.1 (1-Me), 18.1 (Si-C),

16.2 (1-Me), 18.1 (Si-C),

25.7 (Bu^t-Me's), 36.4 (C-2'),

25.8 (Bu^t-Me's), 37.2 (C-2')

71.3 (C-1), 79.3 (C-1'),

70.5 (C-1), 81.3 (C-1'),

116.4 (C-5), 154.3 (C-4),

116.9 (C-5), 154.5 (C-4),

123.8, 127.1, 129.1 (tert.),

123.7, 127.0, 128.9 (tert.)

131.0, 132.8 (tert.).

130.7, 133.3 (tert.).

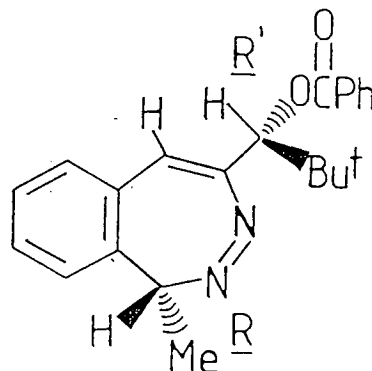
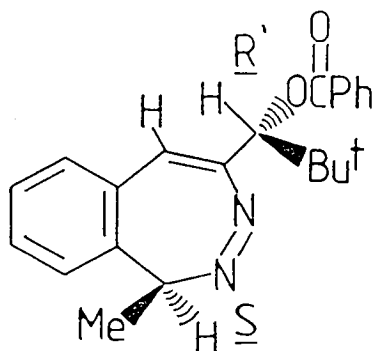
Mass spectral data

301 (5%), 274 (6), 273 (23),
201 (23), 142 (11), 141 (43),
129 (7), 115 (9), 75 (34),
73 (100), 57 (81).

301 (18%), 273 (74), 201 (43),
142 (12), 141 (13), 129 (8),
115 (9), 73 (100), 57 (15).

Appendix 1

Table 8

1-Methyl-4-(2',2'-dimethylprop-1'-yl benzoate)-1H-2,3-benzodiazepine

Product: Major (88)

Minor (87)

¹H N.m.r. spectral data

	(200MHz; CDCl ₃)	(200MHz; CDCl ₃)
<u>tert</u> -Butyl	1.08 (9H, s)	1.17 (9H, s)
1-Me	2.31 (3H, d, J6.6Hz)	2.34 (3H, d, J6.6Hz)
1-H	2.80 (1H, q, J6.6Hz)	2.82 (1H, q, J6.6Hz)
1'-H	6.26 (1H, s)	5.55 (1H, s)
5-H	6.75 (1H, s)	6.79 (1H, s)
Aromatic	7.33-7.67 (7H, m)	7.36-7.66 (4H, m)
Aromatic	8.18 (2H, m)	8.14 (2H, m)

¹³C N.m.r. spectral data

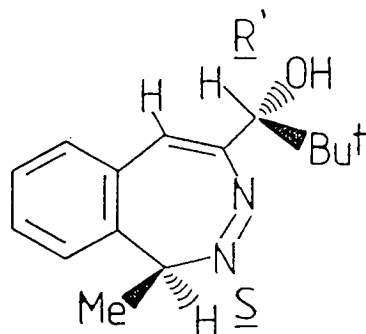
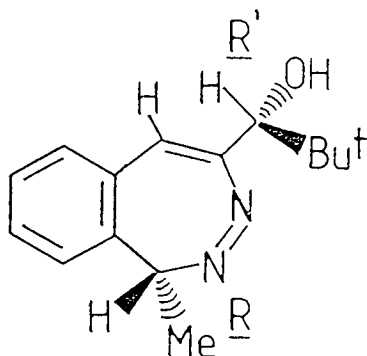
(50MHz; CDCl ₃)	(50MHz; CDCl ₃)
16.0 (1-Me), 26.2 (Bu ^t -Me's),	16.1 (1-Me), 26.6 (Bu ^t -Me's)
35.8 (C-2'), 71.5 (C-1),	35.5 (C-2'), 71.1 (C-1),
81.1 (C-1'), 116.4 (C-5),	82.4 (C-1'), 117.8 (C-5),
150.7 (C-4), 165.2 (C=O),	150.3 (C-4), 165.9 (C=O),
123.8, 127.1, 128.5, 129.9	123.8, 127.0, 128.2, 129.4
(tert.), 130.2 (tert.),	(tert.), 129.6, 130.3
131.3, 132.5 (tert.), 133.1.	(tert.), 131.1, 132.8, 132.9

Mass spectral data

264 (6%), 263 (7), 215 (6),	264 (6%), 263 (8), 215 (6),
198 (11), 183 (18), 155 (13),	198 (8), 183 (15), 155 (12),
142 (11), 129 (13), 106 (38),	142 (8), 129 (10), 119 (31)
105 (100).	106 (27), 105 (100).

Appendix 1

Table 9

1-Methyl-4-(1'-hydroxy-2',2'-trimethylpropyl)-1H-2,3-benzodiazepine

Product:

(90)

(91)

¹H N.m.r. spectral data

	(200MHz; CDCl ₃)	(200MHz; CDCl ₃)
<u>tert</u> -Butyl	0.88 (9H,s)	0.92 (9H,s)
1-Me	2.34 (3H,d,J6.6Hz)	2.31 (3H,d,J6.6Hz)
1-H	2.72 (1H,q,J6.6Hz)	2.73 (1H,q,J6.6Hz)
1'-H	4.31 (1H,s)	4.97 (1H,s)
5-H	6.65 (1H,s)	6.94 (1H,s)
Aromatic	7.36-7.71 (4H,m)	7.35-7.65 (4H,m)
		2.15 (1H, br s, OH)

¹³C N.m.r. spectral data

(50MHz; CDCl ₃)	(50MHz; CDCl ₃)
16.1 (1-Me), 25.7 (Bu ^t -Me's), 35.9 (C-2'), 71.5 (C-1), 82.6 (C-1'), 118.2 (C-5), 151.7 (C-4), 123.8, 127.2, 128.1, 128.7 (tert.), 131.4, 132.8 (tert.).	16.1 (1-Me), 25.8 (Bu ^t -Me's), 35.9 (C-2'), 71.4 (C-1), 79.1 (C-1'), 115.9 (C-5), 154.7 (C-4), 123.8, 127.2, 128.3, 129.2 (tert.), 130.2, 132.8 (tert.).

Mass spectral data

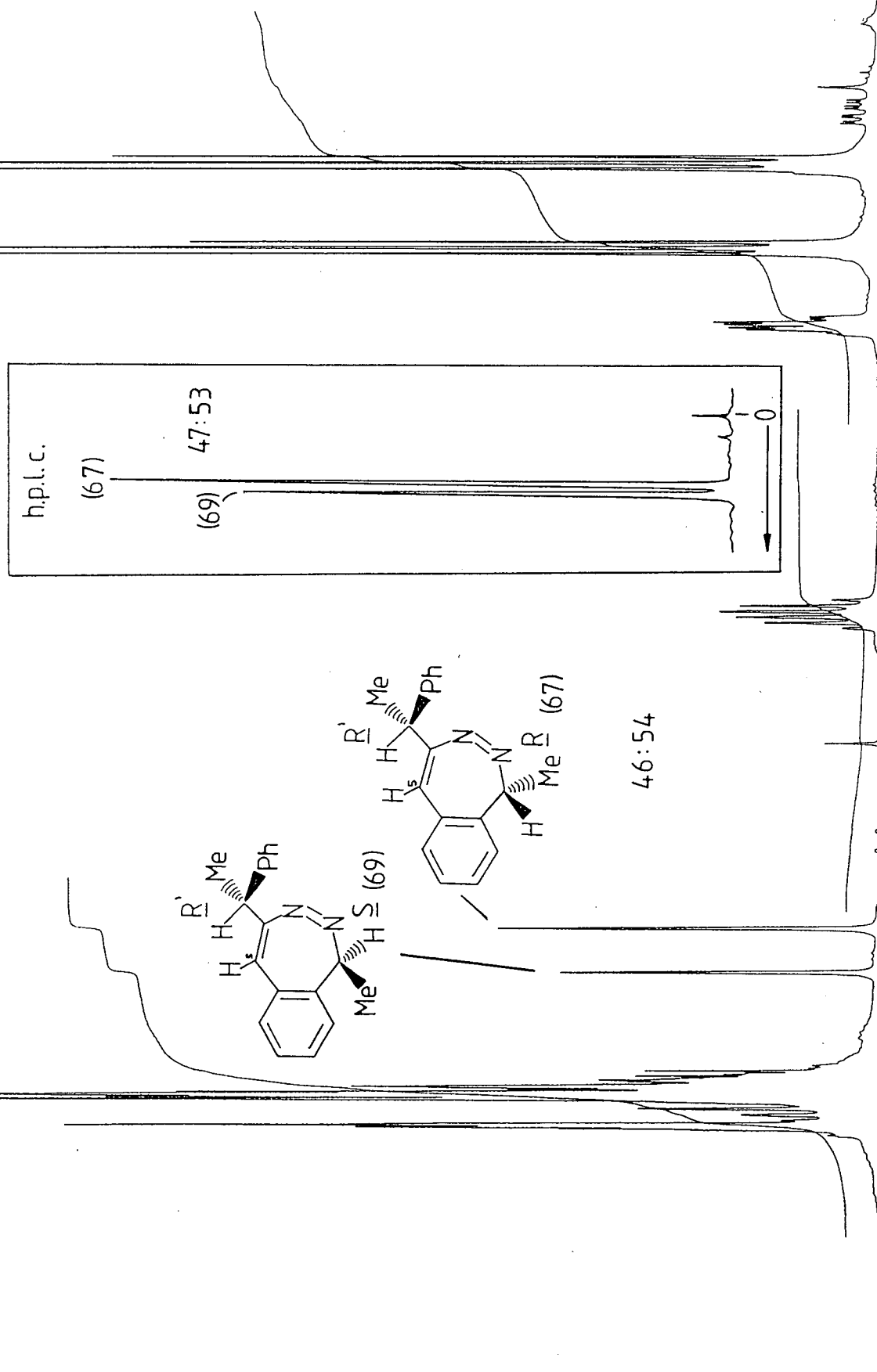
187 (4%), 160 (18), 159 (100), 144 (12), 141 (11), 131 (28), 130 (31), 129 (38), 115 (47), 91 (16).	244 (3%), 196 (7), 160 (13), 159 (100), 145 (6), 144 (9), 130 (26), 129 (31), 115 (36).
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Infrared spectral data (Nujol)3360 cm⁻¹ (OH)3400 cm⁻¹ (OH)

Appendix 2

Diagram 1

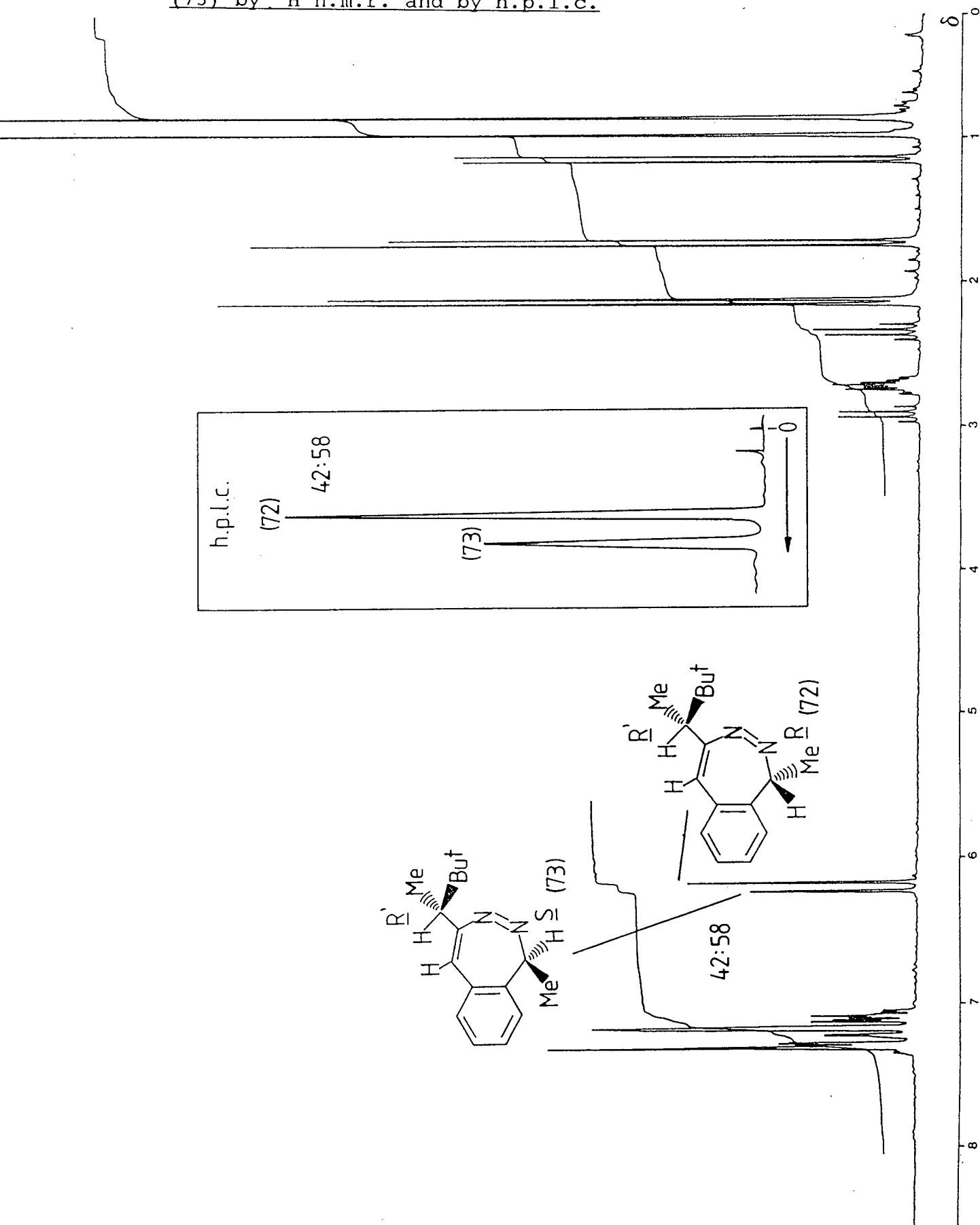
Measurement of the diastereomer ratio of 1-methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepine's (67) and (69) by ^1H n.m.r. and by h.p.l.c..



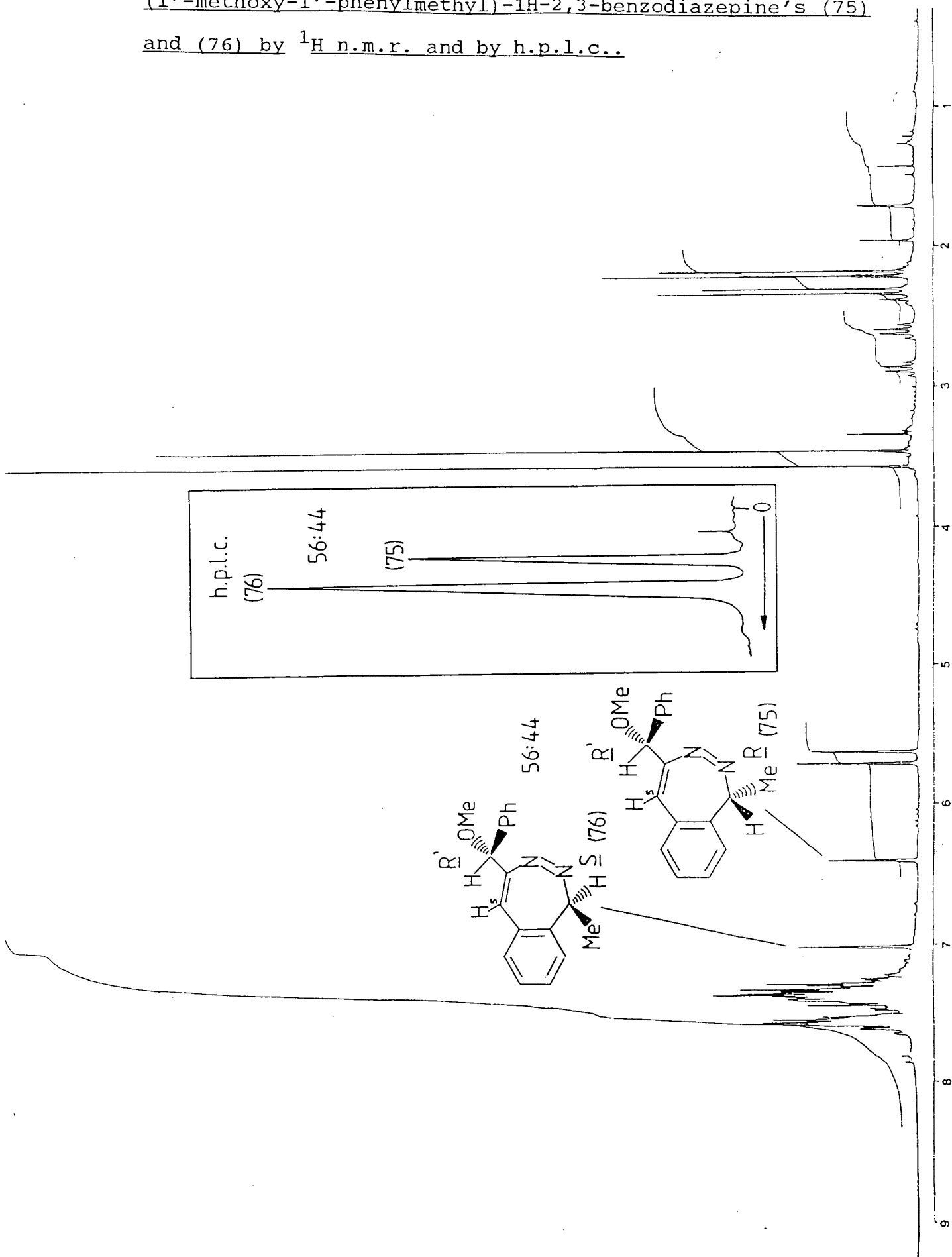
Appendix 2

Diagram 2

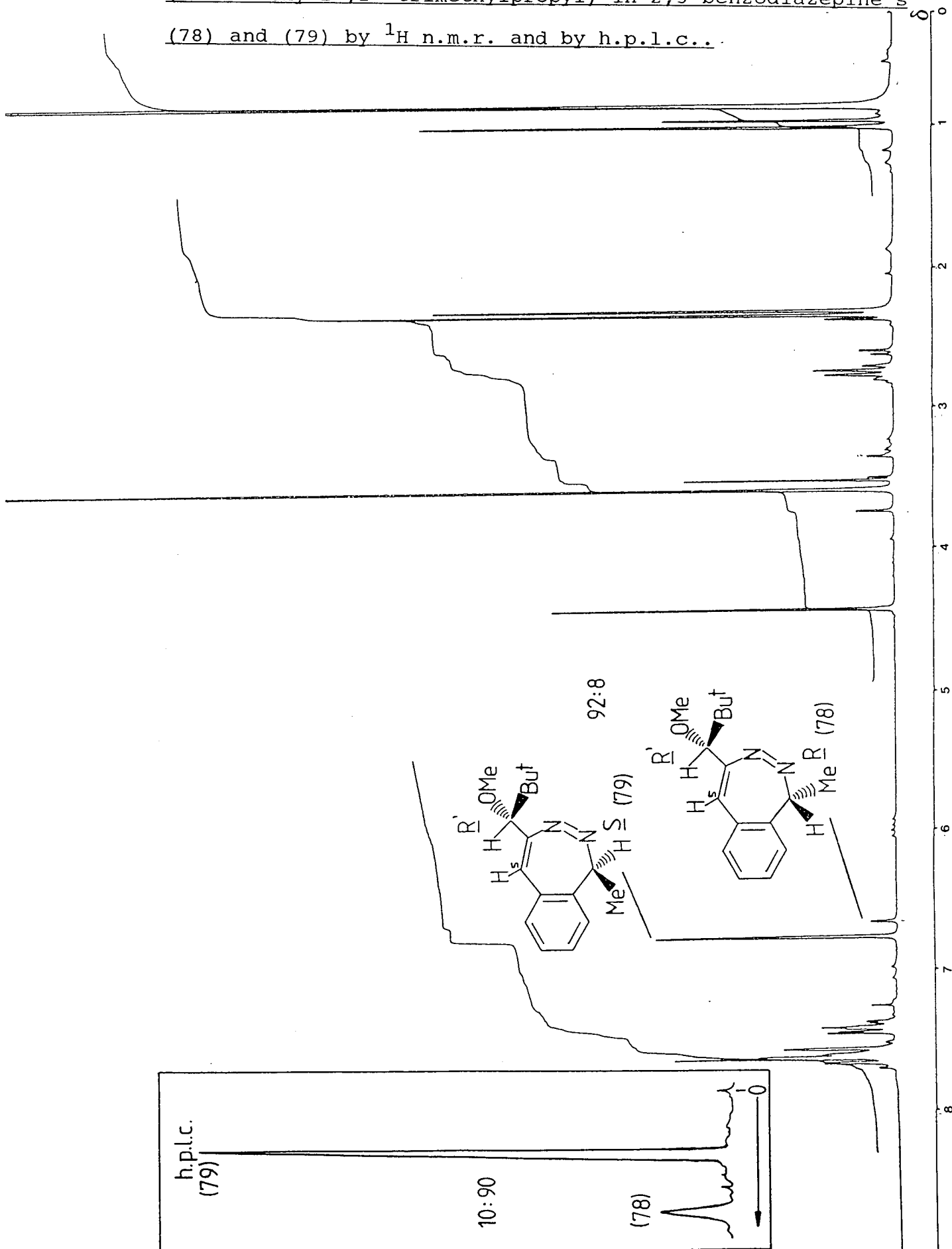
Measurement of the diastereomer ratio of 1-methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepine's (72) and (73) by ^1H n.m.r. and by h.p.l.c.



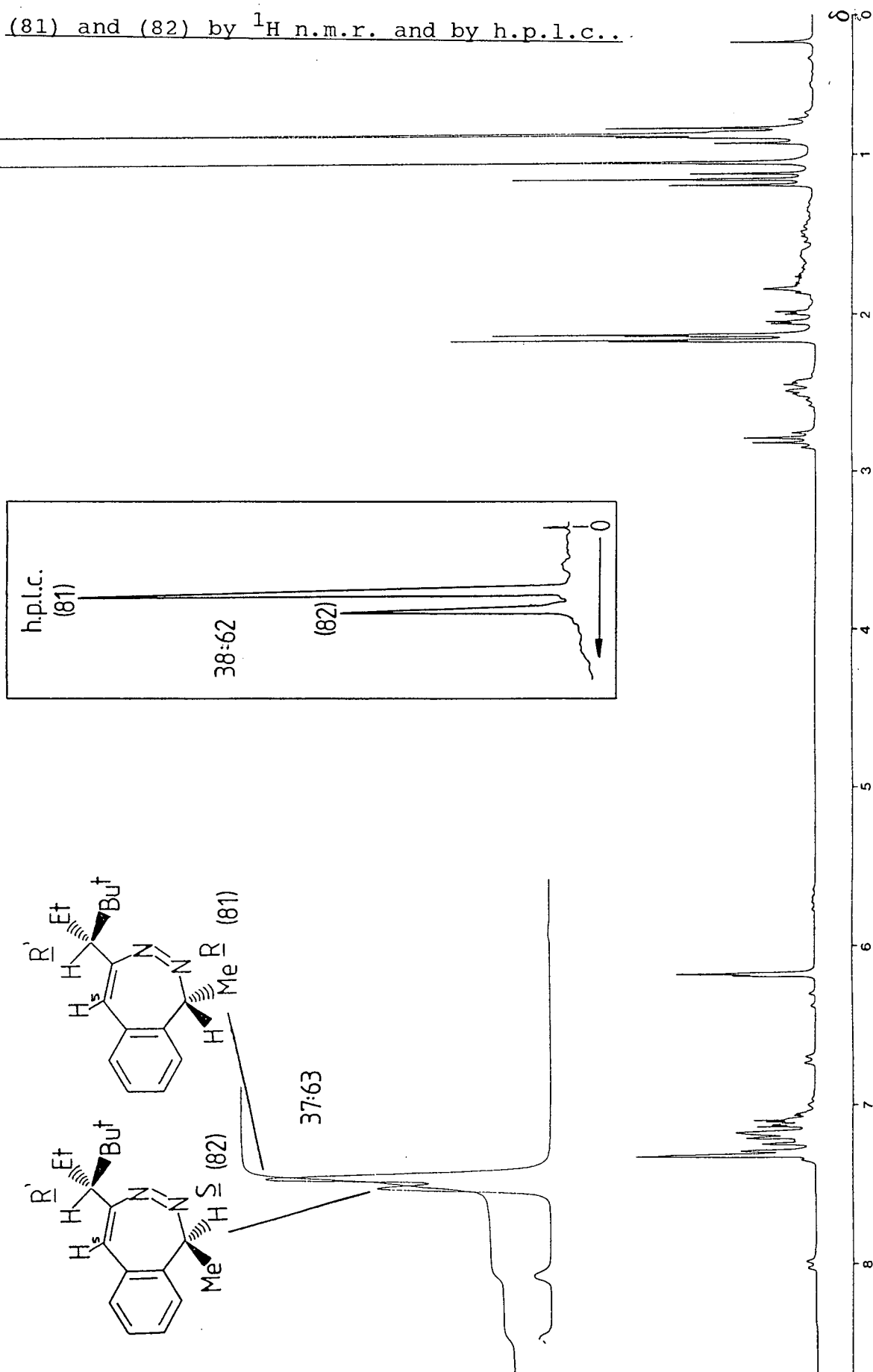
Measurement of the diastereomer ratio of 1-methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepine's (75) and (76) by ^1H n.m.r. and by h.p.l.c..



Measurement of the diastereomer ratio of 1-methyl-4-(1'-methoxy-2',2'-trimethylpropyl)-1H-2,3-benzodiazepine's (78) and (79) by ¹H n.m.r. and by h.p.l.c...



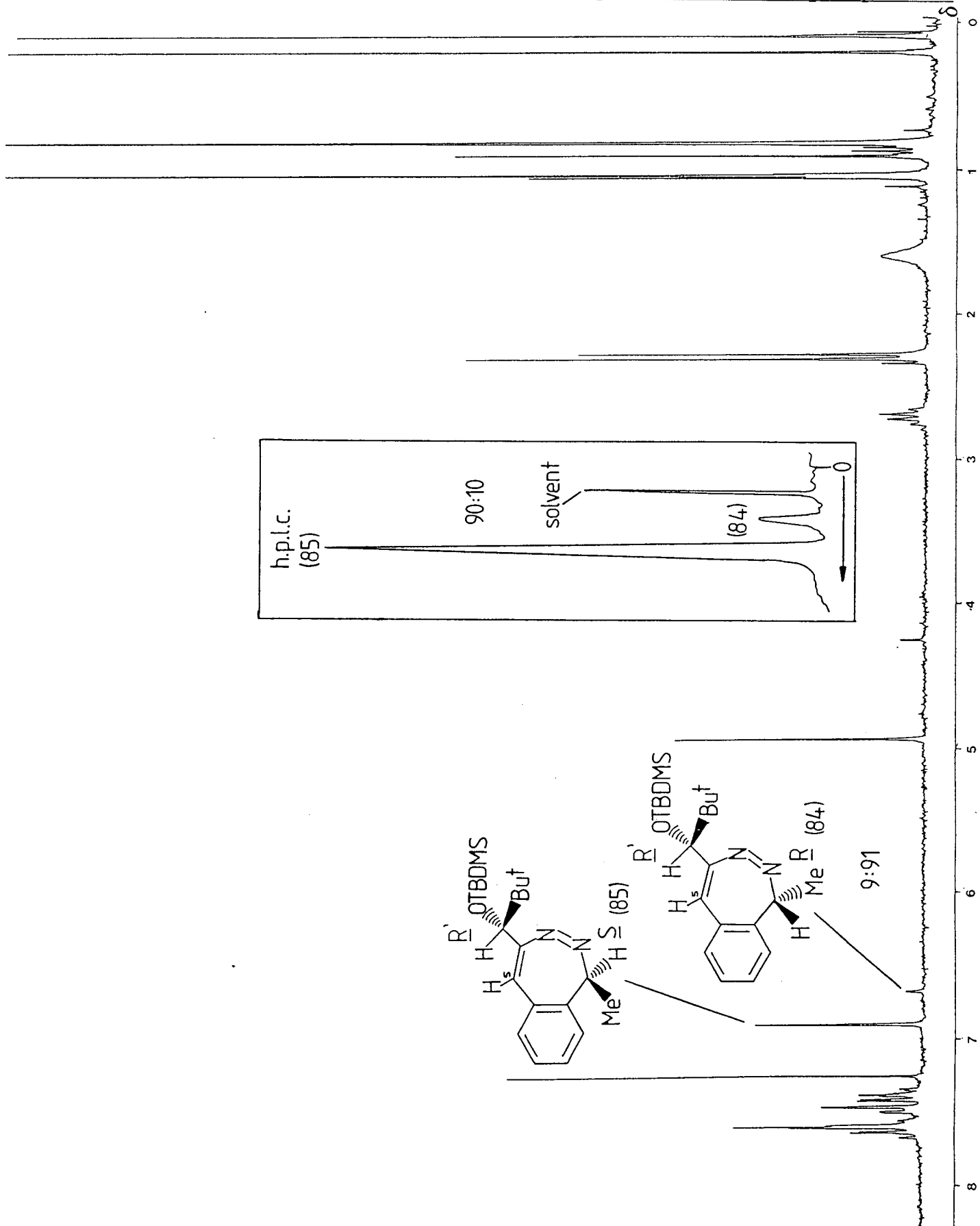
Measurement of the diastereomer ratio of 1-methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine's (81) and (82) by ^1H n.m.r. and by h.p.l.c...



Appendix 2

Diagram 6

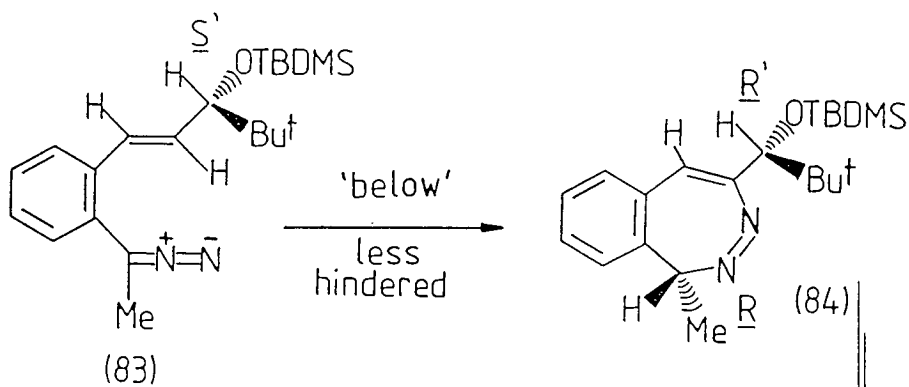
Measurement of the diastereomer ratio of 1-methyl-4-[1'-(tert-butyl dimethylsilyloxy)-2',2'-dimethylpropyl]-1H-2,3-benzodiazepine's (84) and (85) by ^1H n.m.r. and by h.p.l.c..



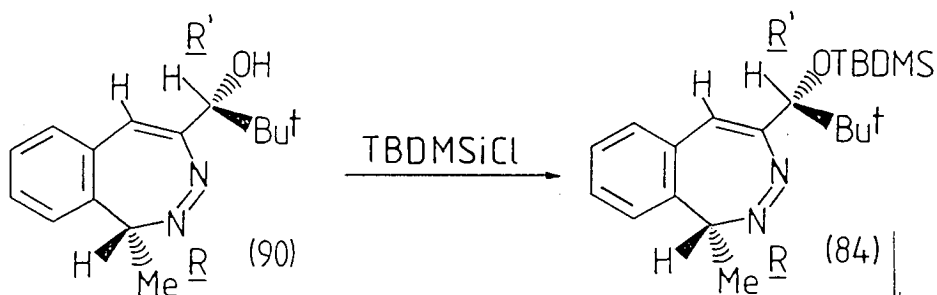
Appendix 2

Diagram 7

^1H N.m.r. spectra of 1H-2,3-benzodiazepine (84) synthesised by the 1,7-electrocyclisation of diazoalkane (83).



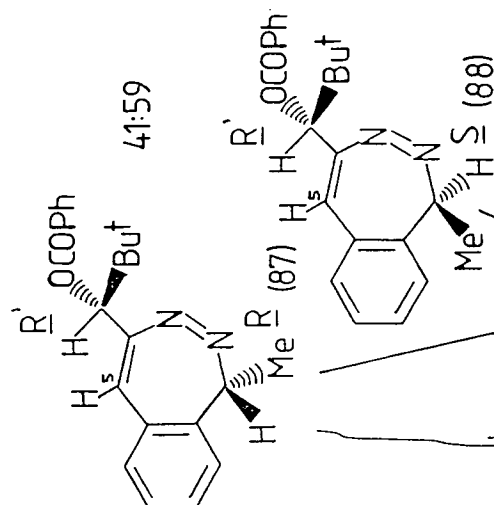
^1H N.m.r. spectra of (84) synthesised by the silylation of 1-methyl-4-(1'-hydroxy-2',2'-trimethylpropyl)-1H-2,3-benzodiazepine (90).



Appendix 2

Diagram 8

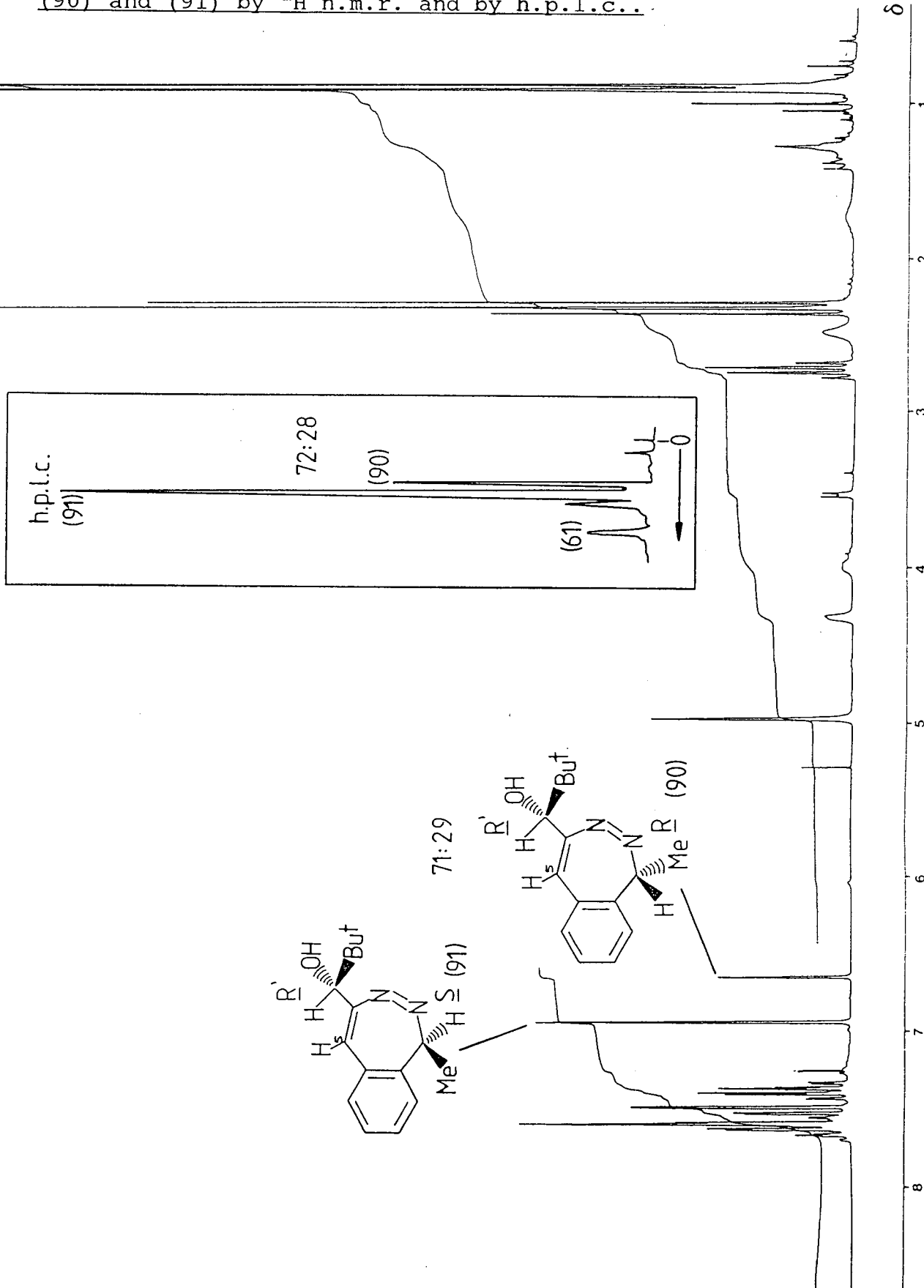
Measurement of the diastereomer ratio of 1-methyl-4-(2',2'-dimethylprop-1'-yl benzoate)-1H-2,3-benzodiazepine's (87) and (88) by ^1H n.m.r..



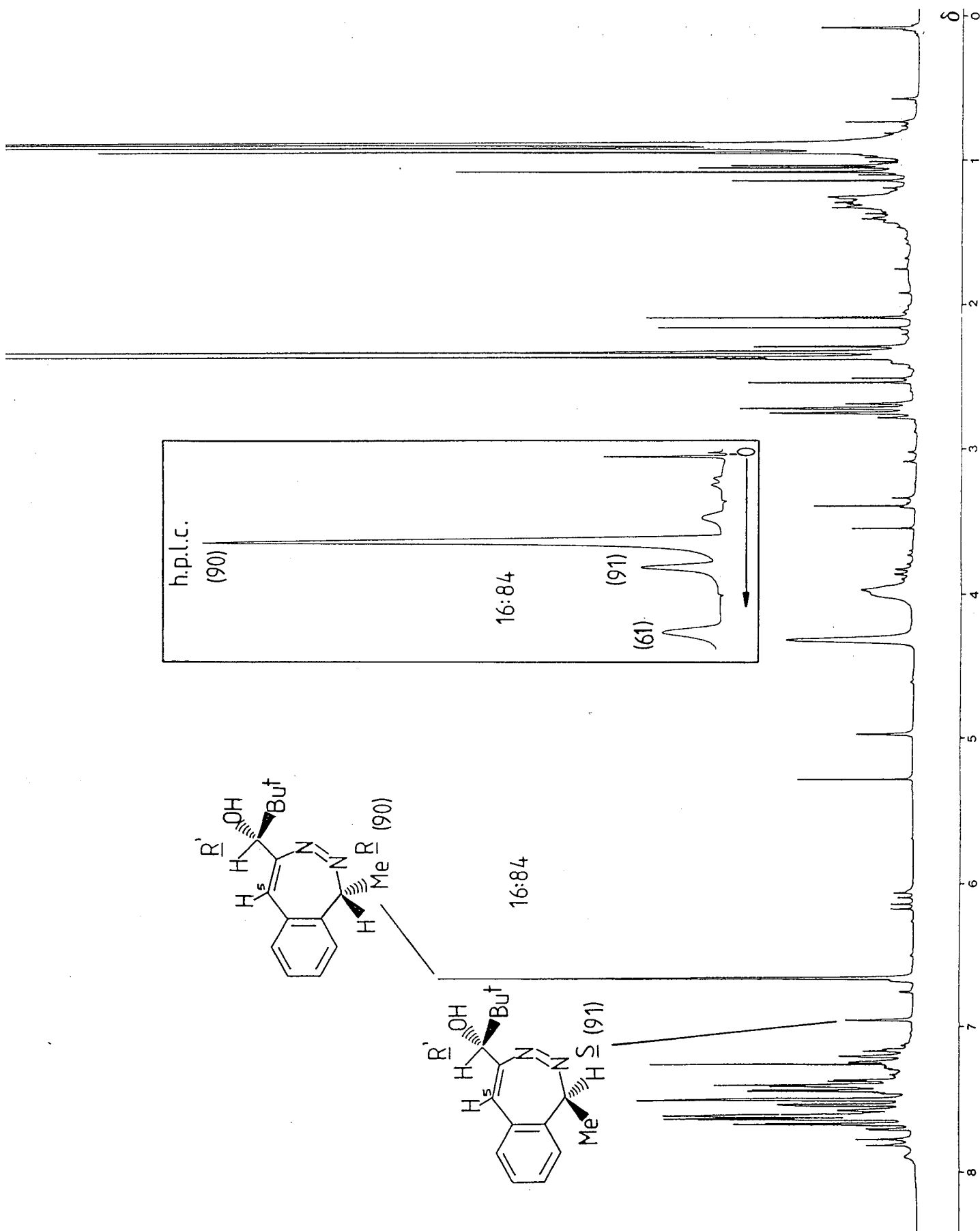
Appendix 2

Diagram 9

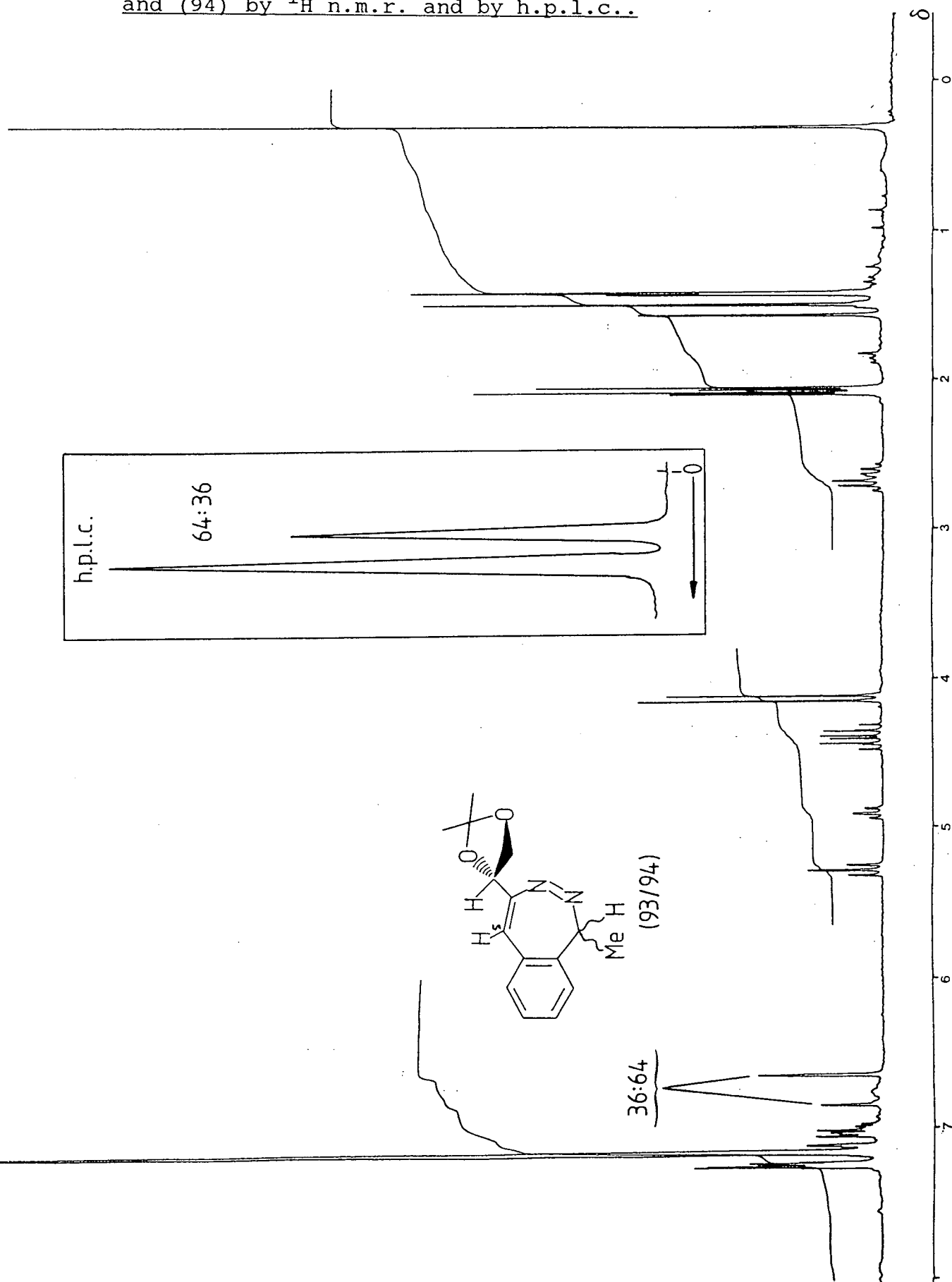
Measurement of the diastereomer ratio of 1-methyl-4-(1'-hydroxy-2',2'-trimethylpropyl)-1H-2,3-benzodiazepine's (90) and (91) by ^1H n.m.r. and by h.p.l.c...



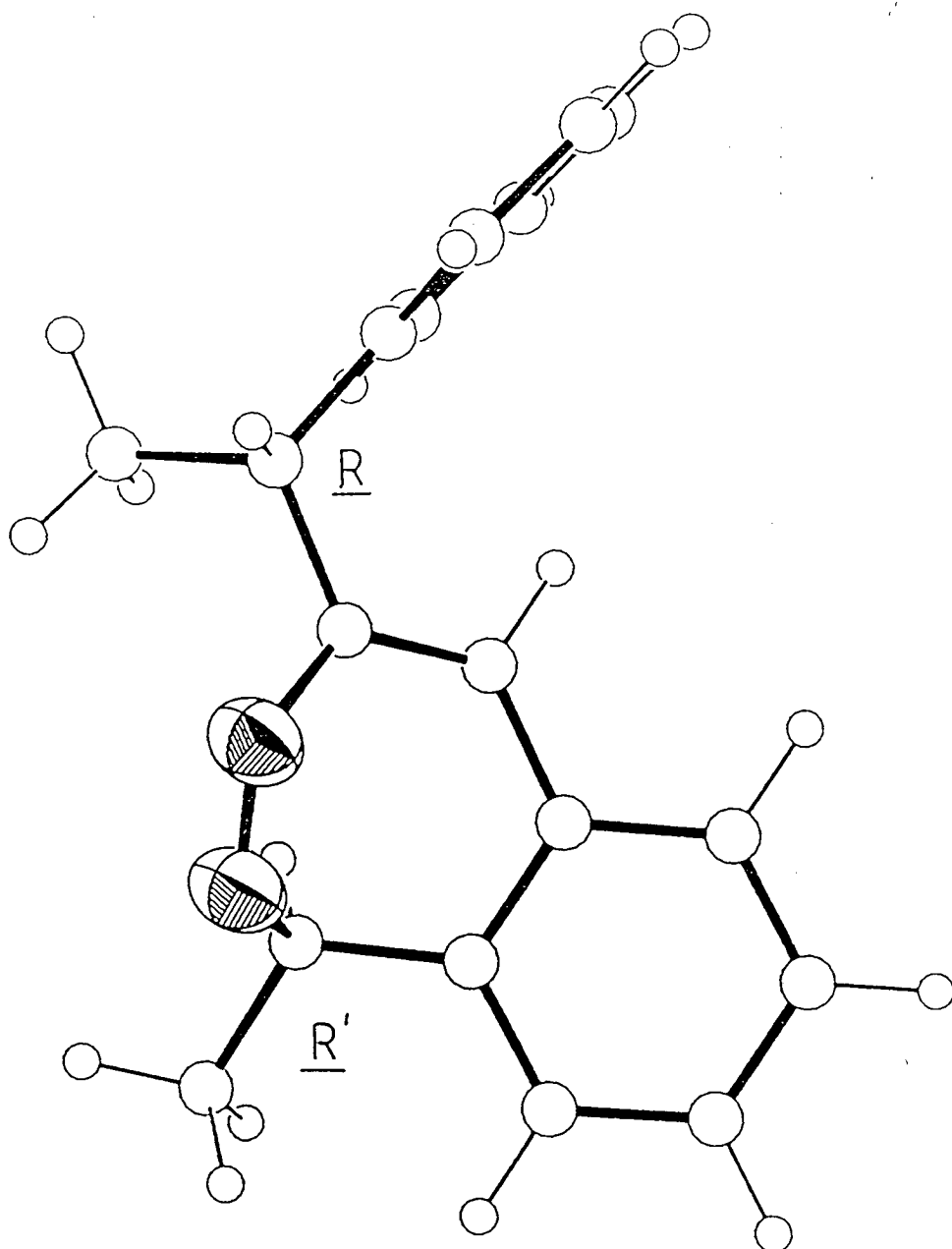
Measurement of the diastereomer ratio of 1-methyl-4-(1'-hydroxy-2',2'-trimethylpropyl)-1H-2,3-benzodiazepine's (90) and (91) by ^1H n.m.r. and by h.p.l.c..



Measurement of the diastereomer ratio of 1-Methyl-4-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-1H-2,3-benzodiazepine's (93) and (94) by ^1H n.m.r. and by h.p.l.c..



1-Methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepine (67).



Appendix 3

Picture 1 (continued)

1-Methyl-4-(1'-phenylethyl)-1H-2,3-benzodiazepine (67).

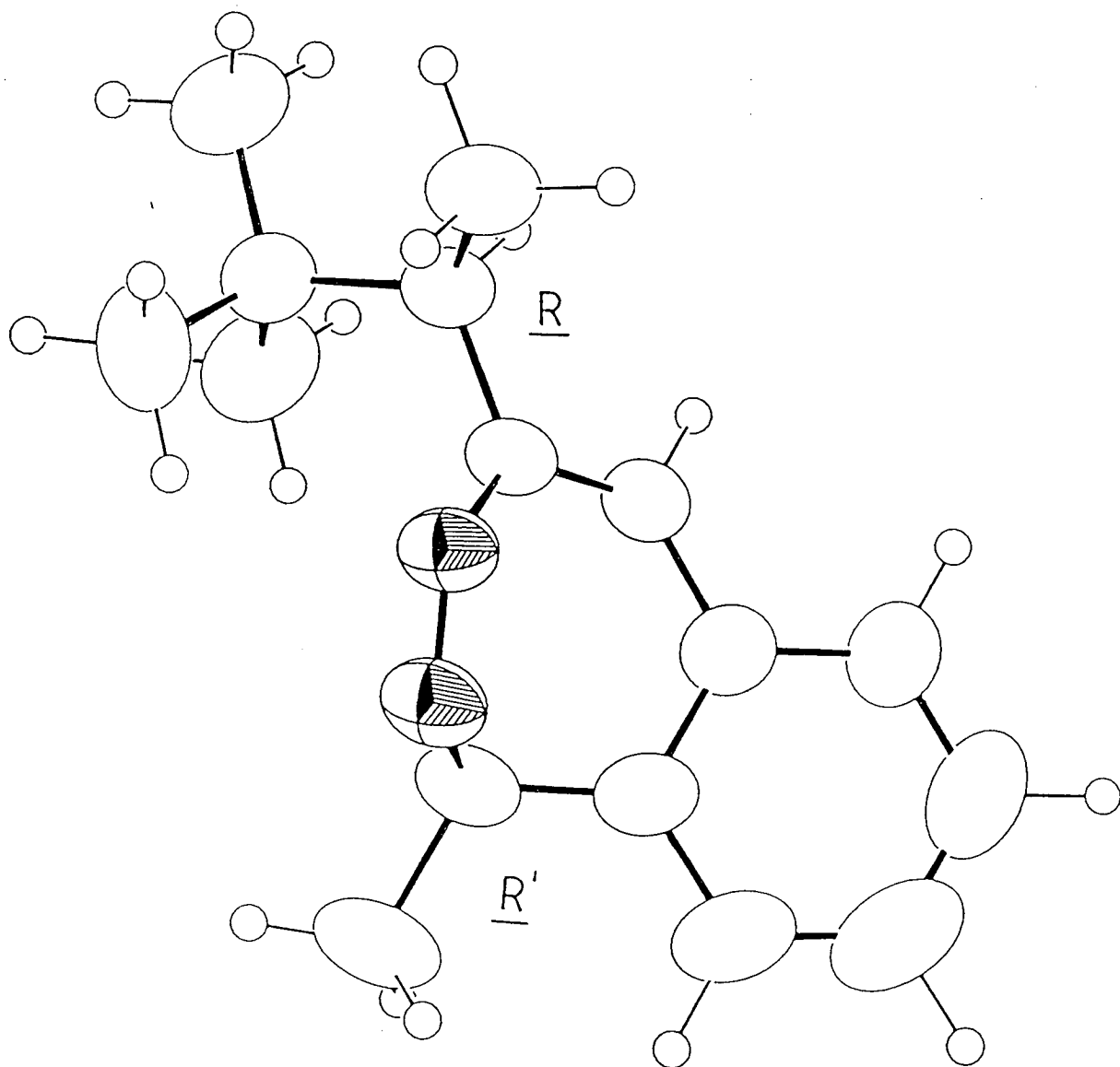
Table 1 . Bond Lengths(A), angles(degrees) and torsion angles(degrees) with standard deviations

C(1) -C(1A)	1.527(4)	C(4A) -C(1P)	1.522(3)
C(1) - N(2)	1.490(3)	C(5) -C(5a)	1.455(4)
C(1) -C(9a)	1.495(4)	C(5a) - C(6)	1.402(4)
N(2) - N(3)	1.256(3)	C(5a) -C(9a)	1.406(4)
N(3) - C(4)	1.419(3)	C(6) - C(7)	1.375(4)
C(4) -C(4A)	1.524(4)	C(7) - C(8)	1.384(4)
C(4) - C(5)	1.348(4)	C(8) - C(9)	1.381(4)
C(4A) -C(4B)	1.534(4)	C(9) -C(9a)	1.399(4)
C(1A) - C(1) - N(2)	108.53(21)	C(5) -C(5a) - C(6)	119.74(23)
C(1A) - C(1) -C(9a)	116.19(22)	C(5) -C(5a) -C(9a)	121.03(23)
N(2) - C(1) -C(9a)	105.16(20)	C(6) -C(5a) -C(9a)	119.22(23)
C(1) - N(2) - N(3)	118.14(21)	C(5a) - C(6) - C(7)	121.1(3)
N(2) - N(3) - C(4)	124.37(22)	C(6) - C(7) - C(8)	119.4(3)
N(3) - C(4) -C(4A)	110.95(21)	C(7) - C(8) - C(9)	120.8(3)
N(3) - C(4) - C(5)	122.59(23)	C(8) - C(9) -C(9a)	120.5(3)
C(4A) - C(4) - C(5)	124.70(23)	C(1) -C(9a) -C(5a)	117.68(22)
C(4) -C(4A) -C(4B)	110.59(22)	C(1) -C(9a) - C(9)	123.51(23)
C(4) -C(4A) -C(1P)	113.42(19)	C(5a) -C(9a) - C(9)	118.81(24)
C(4B) -C(4A) -C(1P)	112.33(20)	C(4A) -C(1P) -C(2P)	120.86(15)
C(4) - C(5) -C(5a)	126.76(24)	C(4A) -C(1P) -C(6P)	119.08(15)
C(1A) - C(1) - N(2) - N(3)	-156.30(23)	C(4B) -C(4A) -C(1P) -C(2P)	-49.4(3)
C(9a) - C(1) - N(2) - N(3)	78.7(3)	C(4B) -C(4A) -C(1P) -C(6P)	133.45(20)
C(1A) - C(1) -C(9a) -C(5a)	168.49(24)	C(4) - C(5) -C(5a) - C(6)	-149.9(3)
C(1A) - C(1) -C(9a) - C(9)	-12.5(4)	C(4) - C(5) -C(5a) -C(9a)	28.8(4)
N(2) - C(1) -C(9a) -C(5a)	-71.5(3)	C(5) -C(5a) - C(6) - C(7)	175.6(3)
N(2) - C(1) -C(9a) - C(9)	107.5(3)	C(9a) -C(5a) - C(6) - C(7)	-3.0(4)
C(1) - N(2) - N(3) - C(4)	-7.6(4)	C(5) -C(5a) -C(9a) - C(1)	5.3(4)
N(2) - N(3) - C(4) -C(4A)	148.67(24)	C(5) -C(5a) -C(9a) - C(9)	-173.74(24)
N(2) - N(3) - C(4) - C(5)	-45.8(4)	C(6) -C(5a) -C(9a) - C(1)	-176.06(24)
N(3) - C(4) -C(4A) -C(4B)	-70.8(3)	C(6) -C(5a) -C(9a) - C(9)	4.9(4)
N(3) - C(4) -C(4A) -C(1P)	161.97(19)	C(5a) - C(6) - C(7) - C(8)	-0.6(4)
C(5) - C(4) -C(4A) -C(4B)	124.0(3)	C(6) - C(7) - C(8) - C(9)	2.3(5)
C(5) - C(4) -C(4A) -C(1P)	-3.2(4)	C(7) - C(8) - C(9) -C(9a)	-0.3(4)
N(3) - C(4) - C(5) -C(5a)	13.0(4)	C(8) - C(9) -C(9a) - C(1)	177.7(3)
C(4A) - C(4) - C(5) -C(5a)	176.57(24)	C(8) - C(9) -C(9a) -C(5a)	-3.3(4)
C(4) -C(4A) -C(1P) -C(2P)	76.88(24)	C(4A) -C(1P) -C(2P) -C(3P)	-177.08(16)
C(4) -C(4A) -C(1P) -C(6P)	-100.24(21)	C(4A) -C(1P) -C(6P) -C(5P)	177.13(16)

Appendix 3

Picture 2

1-Methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepine
(72).



1-Methyl-4-(1',2',2'-trimethylpropyl)-1H-2,3-benzodiazepine
(72).

Table 2 . Bond Lengths(A) with standard deviations

C(1) -C(11)	1.531(6)	C(43) -C(45)	1.521(6)
C(1) - N(2)	1.492(5)	C(43) -C(46)	1.527(6)
C(1) -C(1a)	1.492(5)	C(5) -C(5a)	1.446(5)
N(2) - N(3)	1.247(4)	C(5a) - C(6)	1.404(5)
N(3) - C(4)	1.419(4)	C(5a) -C(1a)	1.404(5)
C(4) -C(41)	1.510(5)	C(6) - C(7)	1.369(7)
C(4) - C(5)	1.355(5)	C(7) - C(8)	1.384(8)
C(41) -C(42)	1.531(5)	C(8) - C(9)	1.364(7)
C(41) -C(43)	1.563(5)	C(9) -C(1a)	1.392(6)
C(43) -C(44)	1.528(6)		

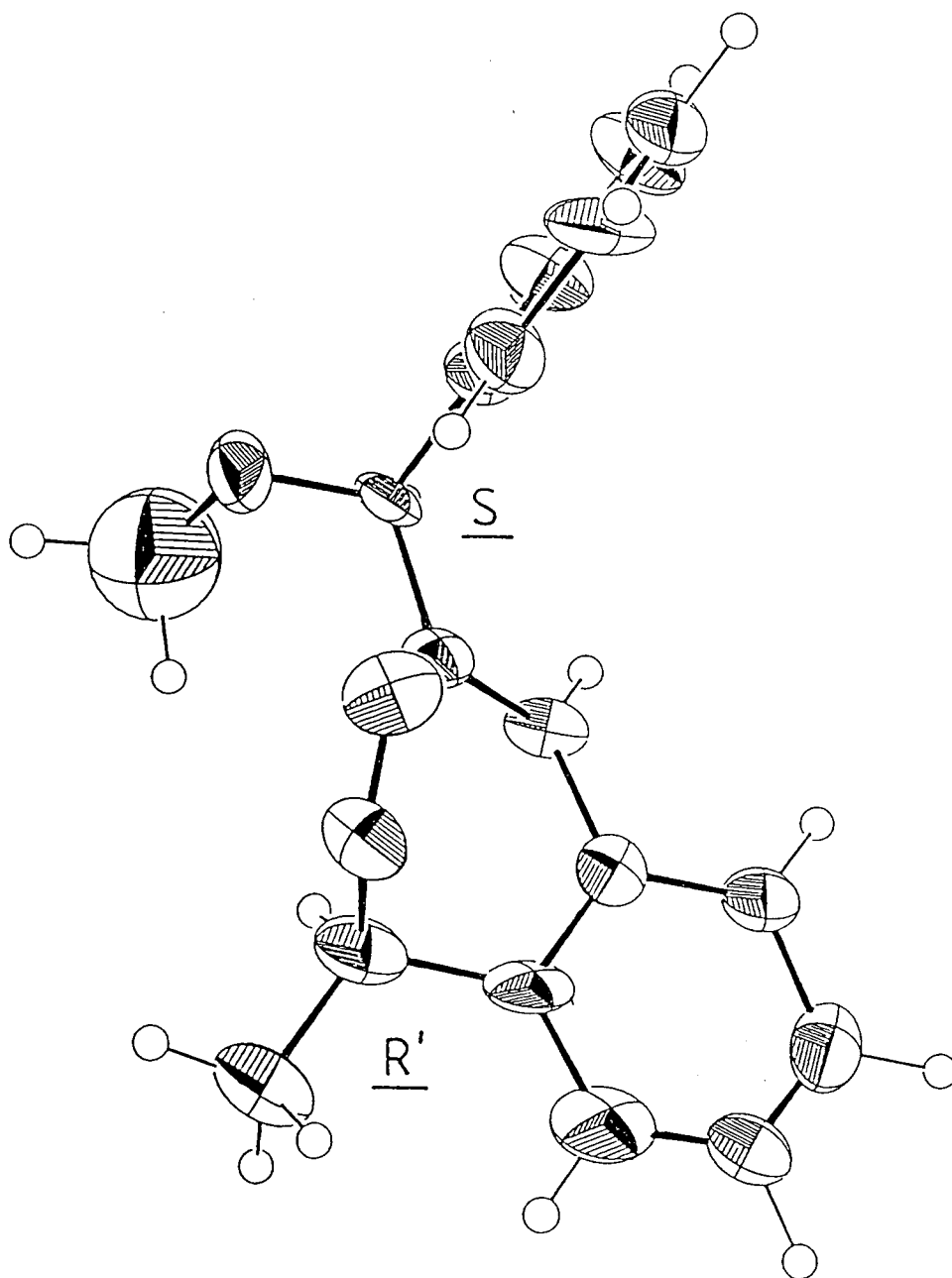
Table 3 . Angles(degrees) with standard deviations

C(11) - C(1) - N(2)	107.6(3)	C(44) -C(43) -C(45)	109.9(3)
C(11) - C(1) -C(1a)	116.7(3)	C(44) -C(43) -C(46)	106.9(3)
N(2) - C(1) -C(1a)	105.1(3)	C(45) -C(43) -C(46)	109.9(3)
C(1) - N(2) - N(3)	118.8(3)	C(4) - C(5) -C(5a)	126.8(3)
N(2) - N(3) - C(4)	124.2(3)	C(5) -C(5a) - C(6)	119.3(3)
N(3) - C(4) -C(41)	114.4(3)	C(5) -C(5a) -C(1a)	121.7(3)
N(3) - C(4) - C(5)	121.5(3)	C(6) -C(5a) -C(1a)	119.0(3)
C(41) - C(4) - C(5)	121.5(3)	C(5a) - C(6) - C(7)	120.2(4)
C(4) -C(41) -C(42)	109.5(3)	C(6) - C(7) - C(8)	120.1(5)
C(4) -C(41) -C(43)	114.6(3)	C(7) - C(8) - C(9)	121.0(5)
C(42) -C(41) -C(43)	114.4(3)	C(8) - C(9) -C(1a)	120.1(4)
C(41) -C(43) -C(44)	108.4(3)	C(1) -C(1a) -C(5a)	116.6(3)
C(41) -C(43) -C(45)	112.6(3)	C(1) -C(1a) - C(9)	123.8(3)
C(41) -C(43) -C(46)	108.9(3)	C(5a) -C(1a) - C(9)	119.6(4)

Table 4 . Torsion angles(degrees) with standard deviations

C(11) - C(1) - N(2) - N(3)	-155.9(3)	C(4) -C(41) -C(43) -C(46)	-171.8(3)
C(1a) - C(1) - N(2) - N(3)	79.2(4)	C(42) -C(41) -C(43) -C(44)	176.5(3)
C(11) - C(1) -C(1a) -C(5a)	170.4(3)	C(42) -C(41) -C(43) -C(45)	-61.7(4)
C(11) - C(1) -C(1a) - C(9)	-9.2(6)	C(42) -C(41) -C(43) -C(46)	60.5(4)
N(2) - C(1) -C(1a) -C(5a)	-70.6(4)	C(4) - C(5) -C(5a) - C(6)	-148.5(4)
N(2) - C(1) -C(1a) - C(9)	109.8(4)	C(4) - C(5) -C(5a) -C(1a)	31.3(6)
C(1) - N(2) - N(3) - C(4)	-6.7(5)	C(5) -C(5a) - C(6) - C(7)	177.6(4)
N(2) - N(3) - C(4) -C(41)	151.9(3)	C(1a) -C(5a) - C(6) - C(7)	-2.2(6)
N(2) - N(3) - C(4) - C(5)	-46.1(5)	C(5) -C(5a) -C(1a) - C(1)	3.4(5)
N(3) - C(4) -C(41) -C(42)	57.0(4)	C(5) -C(5a) -C(1a) - C(9)	-177.0(4)
N(3) - C(4) -C(41) -C(43)	-73.2(4)	C(6) -C(5a) -C(1a) - C(1)	-176.9(3)
C(5) - C(4) -C(41) -C(42)	-104.9(4)	C(6) -C(5a) -C(1a) - C(9)	2.7(6)
C(5) - C(4) -C(41) -C(43)	124.9(4)	C(5a) - C(6) - C(7) - C(8)	0.3(7)
N(3) - C(4) - C(5) -C(5a)	11.9(6)	C(6) - C(7) - C(8) - C(9)	1.0(8)
C(41) - C(4) - C(5) -C(5a)	172.6(3)	C(7) - C(8) - C(9) -C(1a)	-0.4(8)
C(4) -C(41) -C(43) -C(44)	-55.8(4)	C(8) - C(9) -C(1a) - C(1)	178.1(4)
C(4) -C(41) -C(43) -C(45)	66.0(4)	C(8) - C(9) -C(1a) -C(5a)	-1.5(6)

1-Methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepine
(76).



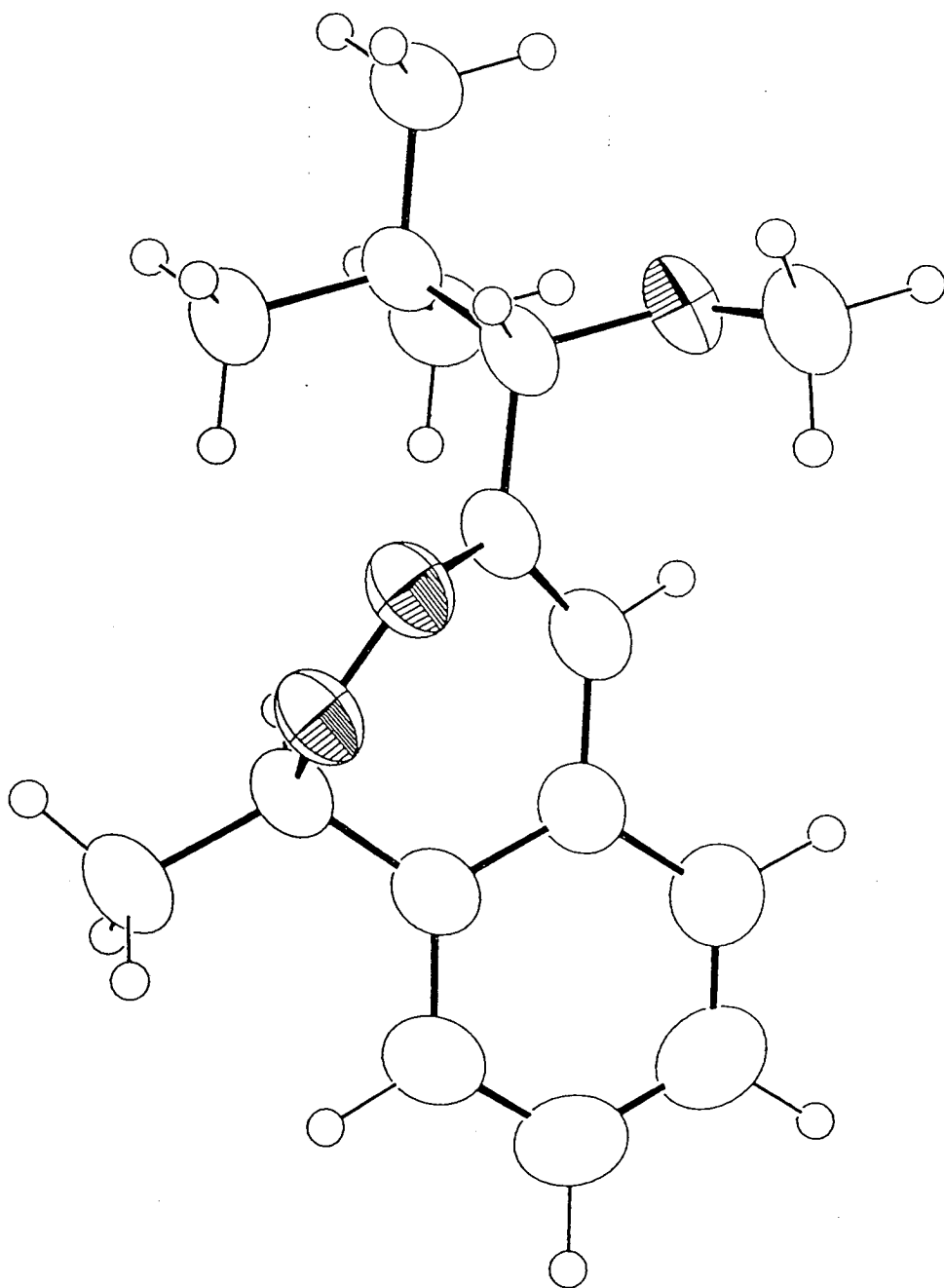
Appendix 3

Picture 3 (continued)

1-Methyl-4-(1'-methoxy-1'-phenylmethyl)-1H-2,3-benzodiazepine
(76).Table 5 . Bond Lengths(A), angles(degrees) and torsion angles(degrees)
with standard deviations

C(1) -C(1M)	1.534(20)	C(5a) -C(9a)	1.436(18)
C(1) - N(2)	1.520(17)	C(6) - C(7)	1.433(20)
C(1) -C(9a)	1.514(19)	C(7) - C(8)	1.248(23)
N(2) - N(3)	1.319(15)	C(8) - C(9)	1.421(23)
N(3) - C(4)	1.385(16)	C(9) -C(9a)	1.370(20)
C(4) - C(5)	1.342(16)	C(41) -O(41)	1.424(16)
C(4) -C(41)	1.533(17)	C(41) -C(1P)	1.510(14)
C(5) -C(5a)	1.448(16)	O(41) -C(42)	1.432(21)
C(5a) - C(6)	1.394(17)		
C(1M) - C(1) - N(2)	104.8(11)	C(6) - C(7) - C(8)	121.6(15)
C(1M) - C(1) -C(9a)	116.1(12)	C(7) - C(8) - C(9)	123.2(16)
N(2) - C(1) -C(9a)	104.1(10)	C(8) - C(9) -C(9a)	118.5(14)
C(1) - N(2) - N(3)	114.5(10)	C(1) -C(9a) -C(5a)	115.7(11)
N(2) - N(3) - C(4)	123.5(10)	C(1) -C(9a) - C(9)	125.2(13)
N(3) - C(4) - C(5)	126.2(11)	C(5a) -C(9a) - C(9)	119.1(12)
N(3) - C(4) -C(41)	111.8(10)	C(4) -C(41) -O(41)	111.4(10)
C(5) - C(4) -C(41)	120.0(11)	C(4) -C(41) -C(1P)	114.3(9)
C(4) - C(5) -C(5a)	125.5(11)	O(41) -C(41) -C(1P)	106.9(9)
C(5) -C(5a) - C(6)	119.6(11)	C(41) -O(41) -C(42)	112.6(11)
C(5) -C(5a) -C(9a)	121.2(11)	C(41) -C(1P) -C(2P)	121.9(7)
C(6) -C(5a) -C(9a)	119.2(11)	C(41) -C(1P) -C(6P)	118.1(7)
C(5a) - C(6) - C(7)	117.7(12)		
C(1M) - C(1) - N(2) - N(3)	-155.5(11)	C(9a) -C(5a) - C(6) - C(7)	-6.1(18)
C(9a) - C(1) - N(2) - N(3)	82.2(12)	C(5) -C(5a) -C(9a) - C(1)	5.7(17)
C(1M) - C(1) -C(9a) -C(5a)	170.6(12)	C(5) -C(5a) -C(9a) - C(9)	-177.2(12)
C(1M) - C(1) -C(9a) - C(9)	-6.2(20)	C(6) -C(5a) -C(9a) - C(1)	-172.5(11)
N(2) - C(1) -C(9a) -C(5a)	-74.8(13)	C(6) -C(5a) -C(9a) - C(9)	4.5(19)
N(2) - C(1) -C(9a) - C(9)	108.4(15)	C(5a) - C(6) - C(7) - C(8)	8.6(22)
C(1) - N(2) - N(3) - C(4)	-10.7(16)	C(6) - C(7) - C(8) - C(9)	-9.1(26)
N(2) - N(3) - C(4) - C(5)	-44.8(18)	C(7) - C(8) - C(9) -C(9a)	7.1(25)
N(2) - N(3) - C(4) -C(41)	151.4(11)	C(8) - C(9) -C(9a) - C(1)	172.2(14)
N(3) - C(4) - C(5) -C(5a)	13.1(20)	C(8) - C(9) -C(9a) -C(5a)	-4.5(21)
C(41) - C(4) - C(5) -C(5a)	175.8(11)	C(4) -C(41) -O(41) -C(42)	-66.9(14)
N(3) - C(4) -C(41) -O(41)	-44.8(13)	C(1P) -C(41) -O(41) -C(42)	167.5(11)
N(3) - C(4) -C(41) -C(1P)	76.6(12)	C(4) -C(41) -C(1P) -C(2P)	-54.6(12)
C(5) - C(4) -C(41) -O(41)	150.2(11)	C(4) -C(41) -C(1P) -C(6P)	124.5(9)
C(5) - C(4) -C(41) -C(1P)	-88.4(13)	O(41) -C(41) -C(1P) -C(2P)	69.3(11)
C(4) - C(5) -C(5a) - C(6)	-151.8(12)	O(41) -C(41) -C(1P) -C(6P)	-111.6(9)
C(4) - C(5) -C(5a) -C(9a)	29.9(18)	C(41) -C(1P) -C(2P) -C(3P)	179.1(8)
C(5) -C(5a) - C(6) - C(7)	175.6(12)	C(41) -C(1P) -C(6P) -C(5P)	-179.2(8)

1-Methyl-4-(1'-methoxy-2',2'-trimethylpropyl)-
1H-2,3-benzodiazepine (79).



Appendix 3

Picture 4 (continued)

1-Methyl-4-(1'-methoxy-2',2'-trimethylpropyl)-
1H-2,3-benzodiazepine (79).

Table 6 . Bond Lengths(A) with standard deviations

C(1) -C(11)	1.526(3)	C(43) -C(44)	1.523(3)
C(1) - N(2)	1.4934(23)	C(43) -C(45)	1.535(3)
C(1) -C(1a)	1.4884(25)	C(43) -C(46)	1.533(3)
N(2) - N(3)	1.2555(21)	C(5) -C(5a)	1.4484(25)
N(3) - C(4)	1.4200(22)	C(5a) - C(6)	1.398(3)
C(4) -C(41)	1.5143(24)	C(5a) -C(1a)	1.4155(25)
C(4) - C(5)	1.3494(24)	C(6) - C(7)	1.373(3)
C(41) -O(41)	1.4285(21)	C(7) - C(8)	1.383(3)
C(41) -C(43)	1.5427(24)	C(8) - C(9)	1.379(3)
O(41) -C(42)	1.4211(25)	C(9) -C(1a)	1.399(3)

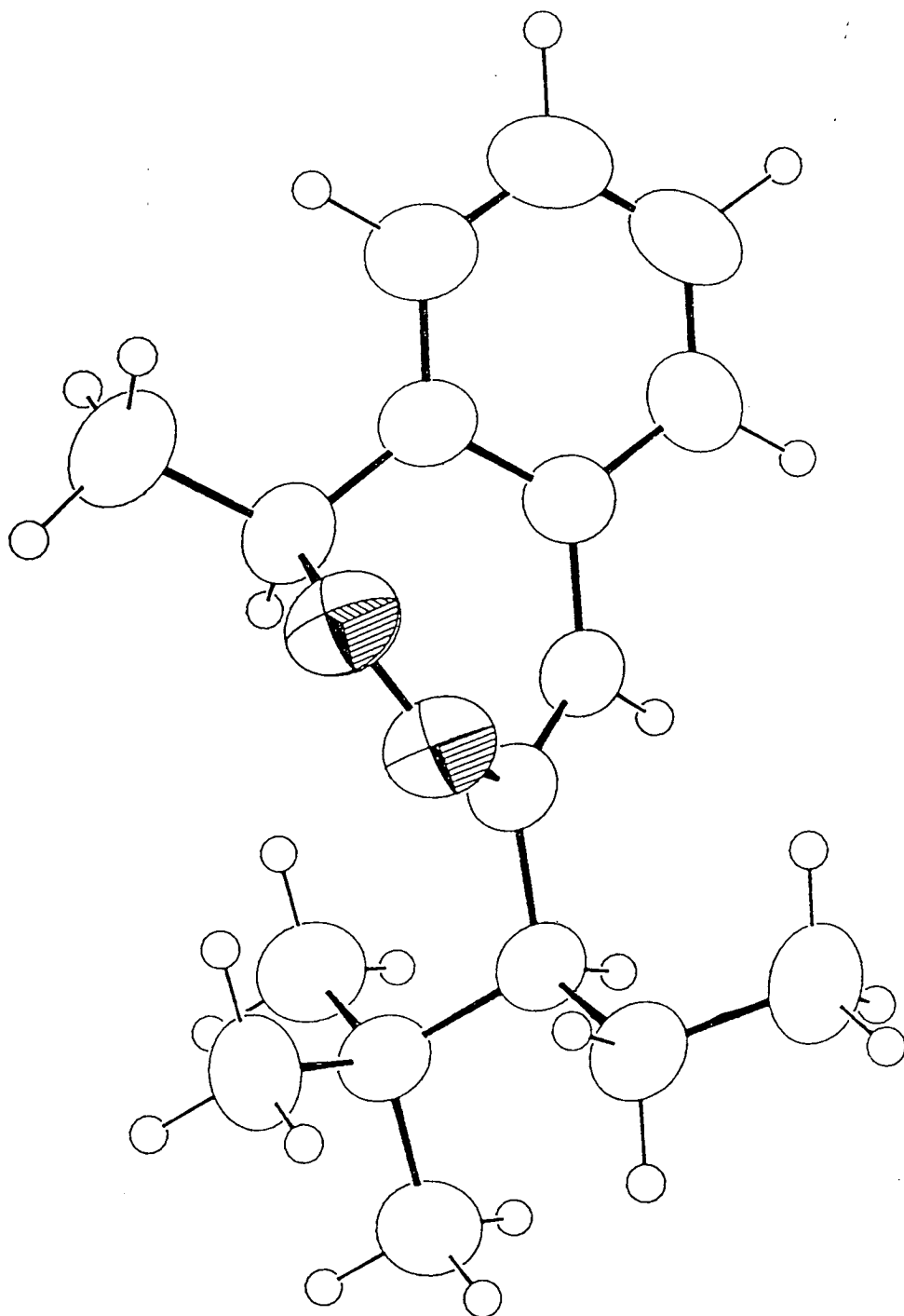
Table 7 . Angles(degrees) with standard deviations

C(11) - C(1) - N(2)	107.71(14)	C(44) -C(43) -C(45)	109.80(15)
C(11) - C(1) -C(1a)	116.69(15)	C(44) -C(43) -C(46)	110.46(15)
N(2) - C(1) -C(1a)	106.35(14)	C(45) -C(43) -C(46)	108.00(15)
C(1) - N(2) - N(3)	117.71(14)	C(4) - C(5) -C(5a)	127.05(16)
N(2) - N(3) - C(4)	124.01(15)	C(5) -C(5a) - C(6)	119.90(17)
N(3) - C(4) -C(41)	112.69(14)	C(5) -C(5a) -C(1a)	121.15(16)
N(3) - C(4) - C(5)	122.23(15)	C(6) -C(5a) -C(1a)	118.93(17)
C(41) - C(4) - C(5)	123.22(15)	C(5a) - C(6) - C(7)	120.84(20)
C(4) -C(41) -O(41)	111.57(14)	C(6) - C(7) - C(8)	120.20(22)
C(4) -C(41) -C(43)	113.89(14)	C(7) - C(8) - C(9)	120.55(21)
O(41) -C(41) -C(43)	107.51(13)	C(8) - C(9) -C(1a)	120.26(19)
C(41) -O(41) -C(42)	113.13(14)	C(1) -C(1a) -C(5a)	117.44(15)
C(41) -C(43) -C(44)	111.08(15)	C(1) -C(1a) - C(9)	123.32(16)
C(41) -C(43) -C(45)	109.04(15)	C(5a) -C(1a) - C(9)	119.19(16)
C(41) -C(43) -C(46)	108.38(14)		

Table 8 . Torsion angles(degrees) with standard deviations

C(11) - C(1) - N(2) - N(3)	154.57(15)	C(4) -C(41) -C(43) -C(45)	-54.84(19)
C(1a) - C(1) - N(2) - N(3)	-79.62(18)	C(4) -C(41) -C(43) -C(46)	-172.17(15)
C(11) - C(1) -C(1a) -C(5a)	-170.70(16)	O(41) -C(41) -C(43) -C(44)	-57.84(18)
C(11) - C(1) -C(1a) - C(9)	6.9(3)	O(41) -C(41) -C(43) -C(45)	-178.99(14)
N(2) - C(1) -C(1a) -C(5a)	69.14(19)	O(41) -C(41) -C(43) -C(46)	63.68(17)
N(2) - C(1) -C(1a) - C(9)'	-113.22(19)	C(4) - C(5) -C(5a) - C(6)	153.84(19)
C(1) - N(2) - N(3) - C(4)	8.50(24)	C(4) - C(5) -C(5a) -C(1a)	-28.1(3)
N(2) - N(3) - C(4) -C(41)	-148.00(16)	C(5) -C(5a) - C(6) - C(7)	179.47(19)
N(2) - N(3) - C(4) - C(5)	47.07(25)	C(1a) -C(5a) - C(6) - C(7)	1.3(3)
N(3) - C(4) -C(41) -O(41)	-137.11(14)	C(5) -C(5a) -C(1a) - C(1)	-2.51(25)
N(3) - C(4) -C(41) -C(43)	100.96(17)	C(5) -C(5a) -C(1a) - C(9)	179.74(17)
C(5) - C(4) -C(41) -O(41)	27.65(23)	C(6) -C(5a) -C(1a) - C(1)	175.61(17)
C(5) - C(4) -C(41) -C(43)	-94.29(20)	C(6) -C(5a) -C(1a) - C(9)	-2.1(3)
N(3) - C(4) - C(5) -C(5a)	-16.4(3)	C(5a) - C(6) - C(7) - C(8)	0.0(3)
C(41) - C(4) - C(5) -C(5a)	-179.70(17)	C(6) - C(7) - C(8) - C(9)	-0.5(4)
C(4) -C(41) -O(41) -C(42)	75.90(18)	C(7) - C(8) - C(9) -C(1a)	-0.4(3)
C(43) -C(41) -O(41) -C(42)	-158.55(15)	C(8) - C(9) -C(1a) - C(1)	-175.94(19)
C(4) -C(41) -C(43) -C(44)	66.31(19)	C(8) - C(9) -C(1a) -C(5a)	1.7(3)

1-Methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-
1H-2,3-benzodiazepine (81).



Appendix 3

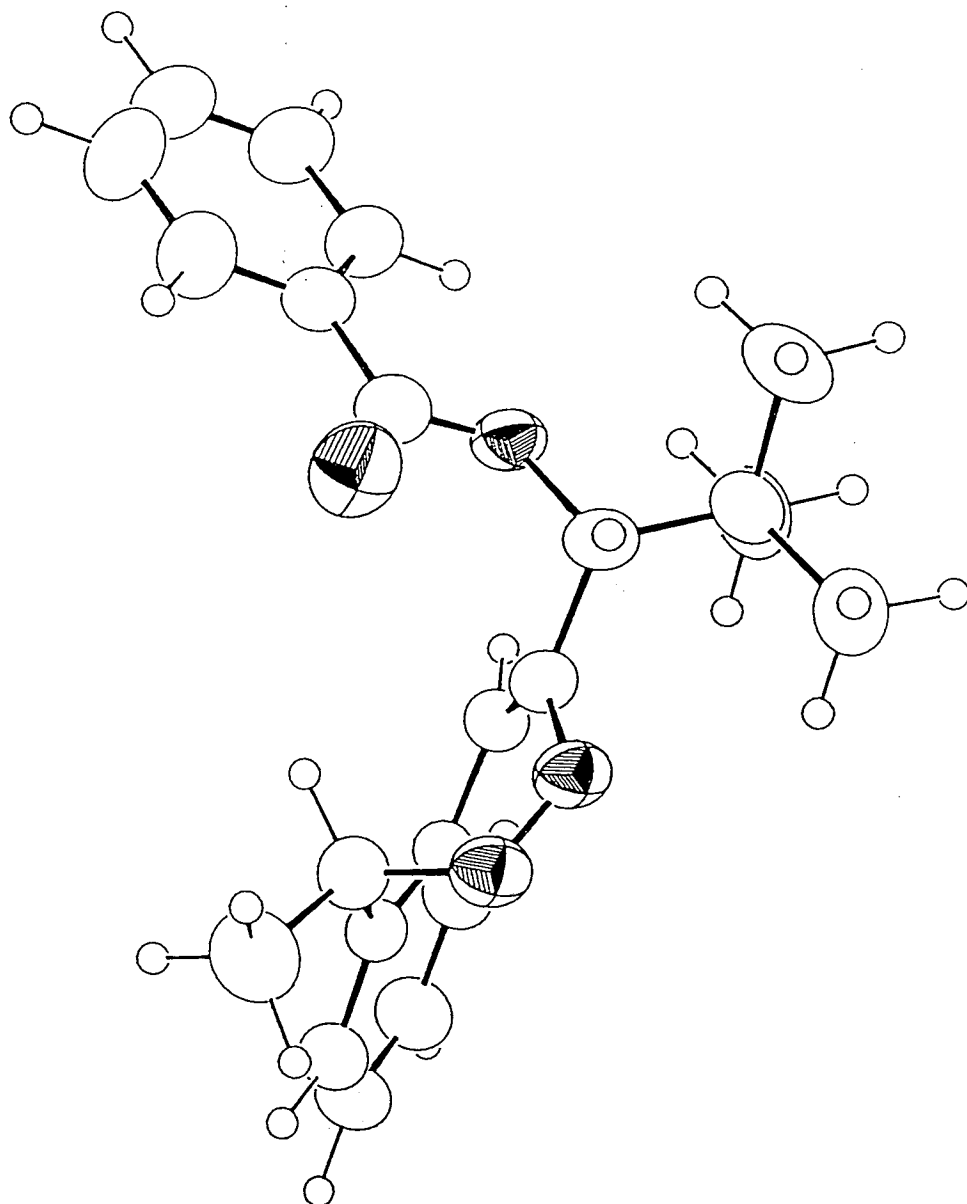
Picture 5 (continued)

1-Methyl-4-(1'-ethyl-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine (81).

Table 9 . Bond Lengths(A), angles(degrees) and torsion angles(degrees) with standard deviations

C(1) -C(1M)	1.524(6)	C(6) - C(7)	1.376(7)
C(1) - N(2)	1.493(6)	C(7) - C(8)	1.384(7)
C(1) -C(1a)	1.495(6)	C(8) - C(9)	1.369(7)
N(2) - N(3)	1.255(5)	C(9) -C(1a)	1.391(6)
N(3) - C(4)	1.421(5)	C(41) -C(42)	1.550(6)
C(4) - C(5)	1.352(5)	C(41) -C(44)	1.557(5)
C(4) -C(41)	1.511(5)	C(42) -C(43)	1.517(6)
C(5) -C(5a)	1.450(5)	C(44) -C(45)	1.544(6)
C(5a) - C(6)	1.407(6)	C(44) -C(46)	1.531(6)
C(5a) -C(1a)	1.410(5)	C(44) -C(47)	1.536(6)
C(1M) - C(1) - N(2)	107.9(3)	C(8) - C(9) -C(1a)	120.7(4)
C(1M) - C(1) -C(1a)	116.1(4)	C(1) -C(1a) -C(5a)	116.6(3)
N(2) - C(1) -C(1a)	105.5(3)	C(1) -C(1a) - C(9)	124.0(4)
C(1) - N(2) - N(3)	117.7(4)	C(5a) -C(1a) - C(9)	119.4(4)
N(2) - N(3) - C(4)	124.2(4)	C(4) -C(41) -C(42)	111.2(3)
N(3) - C(4) - C(5)	121.2(3)	C(4) -C(41) -C(44)	113.6(3)
N(3) - C(4) -C(41)	114.4(3)	C(42) -C(41) -C(44)	113.5(3)
C(5) - C(4) -C(41)	122.5(3)	C(41) -C(42) -C(43)	112.4(3)
C(4) - C(5) -C(5a)	127.2(3)	C(41) -C(44) -C(45)	110.1(3)
C(5) -C(5a) - C(6)	120.1(4)	C(41) -C(44) -C(46)	112.5(3)
C(5) -C(5a) -C(1a)	121.4(3)	C(41) -C(44) -C(47)	109.2(3)
C(6) -C(5a) -C(1a)	118.5(4)	C(45) -C(44) -C(46)	108.6(3)
C(5a) - C(6) - C(7)	121.1(4)	C(45) -C(44) -C(47)	107.1(3)
C(6) - C(7) - C(8)	119.4(5)	C(46) -C(44) -C(47)	109.2(3)
C(7) - C(8) - C(9)	120.9(5)		
C(1M) - C(1) - N(2) - N(3)	154.6(4)	C(1a) -C(5a) - C(6) - C(7)	1.8(6)
C(1a) - C(1) - N(2) - N(3)	-80.7(4)	C(5) -C(5a) -C(1a) - C(1)	-1.6(5)
C(1M) - C(1) -C(1a) -C(5a)	-171.1(4)	C(5) -C(5a) -C(1a) - C(9)	179.4(4)
C(1M) - C(1) -C(1a) - C(9)	7.9(6)	C(6) -C(5a) -C(1a) - C(1)	176.5(4)
N(2) - C(1) -C(1a) -C(5a)	69.6(4)	C(6) -C(5a) -C(1a) - C(9)	-2.5(6)
N(2) - C(1) -C(1a) - C(9)	-111.5(4)	C(5a) - C(6) - C(7) - C(8)	0.1(7)
C(1) - N(2) - N(3) - C(4)	8.5(6)	C(6) - C(7) - C(8) - C(9)	-1.5(8)
N(2) - N(3) - C(4) - C(5)	46.4(6)	C(7) - C(8) - C(9) -C(1a)	0.8(7)
N(2) - N(3) - C(4) -C(41)	-149.0(4)	C(8) - C(9) -C(1a) - C(1)	-177.7(4)
N(3) - C(4) - C(5) -C(5a)	-14.0(6)	C(8) - C(9) -C(1a) -C(5a)	1.2(7)
C(41) - C(4) - C(5) -C(5a)	-177.4(4)	C(4) -C(41) -C(42) -C(43)	-65.0(4)
N(3) - C(4) -C(41) -C(42)	-50.8(4)	C(44) -C(41) -C(42) -C(43)	165.4(3)
N(3) - C(4) -C(41) -C(44)	78.7(4)	C(4) -C(41) -C(44) -C(45)	171.5(3)
C(5) - C(4) -C(41) -C(42)	113.6(4)	C(4) -C(41) -C(44) -C(46)	-67.2(4)
C(5) - C(4) -C(41) -C(44)	-116.8(4)	C(4) -C(41) -C(44) -C(47)	54.2(4)
C(4) - C(5) -C(5a) - C(6)	151.1(4)	C(42) -C(41) -C(44) -C(45)	-60.1(4)
C(4) - C(5) -C(5a) -C(1a)	-30.7(6)	C(42) -C(41) -C(44) -C(46)	61.2(4)
C(5) -C(5a) - C(6) - C(7)	-179.9(4)	C(42) -C(41) -C(44) -C(47)	-177.4(3)

1-Methyl-4-(2',2'-dimethylprop-1'-yl benzoate)-
1H-2,3-benzodiazepine (87).



Appendix 3

Picture 6 (continued)

Table 10 . Bond Lengths(A), angles(degrees) and torsion angles(degrees)
with standard deviations

C(1) -C(1M)	1.514(3)	C(1') -C(2')	1.546(3)
C(1) - N(2)	1.493(3)	C(1') -O(1')	1.4509(24)
C(1) -C(9a)	1.497(3)	C(2') -C(21')	1.532(4)
N(2) - N(3)	1.2590(23)	C(2') -C(22')	1.528(4)
N(3) - C(4)	1.4111(24)	C(2') -C(23')	1.531(4)
C(4) - C(5)	1.347(3)	O(1') -C(3')	1.3428(24)
C(4) -C(1')	1.516(3)	C(3') -O(3')	1.204(3)
C(5) -C(5a)	1.448(3)	C(3') -C(1P)	1.475(3)
C(5a) - C(6)	1.403(3)	C(1P) -C(2P)	1.383(3)
C(5a) -C(9a)	1.403(3)	C(1P) -C(6P)	1.377(3)
C(6) - C(7)	1.366(3)	C(2P) -C(3P)	1.385(4)
C(7) - C(8)	1.384(3)	C(3P) -C(4P)	1.368(4)
C(8) - C(9)	1.386(3)	C(4P) -C(5P)	1.367(4)
C(9) -C(9a)	1.388(3)	C(5P) -C(6P)	1.380(4)
C(1M) - C(1) - N(2)	107.58(17)	C(4) -C(1') -O(1')	108.95(15)
C(1M) - C(1) -C(9a)	115.85(18)	C(2') -C(1') -O(1')	106.50(16)
N(2) - C(1) -C(9a)	105.89(15)	C(1') -C(2') -C(21')	108.16(19)
C(1) - N(2) - N(3)	117.31(16)	C(1') -C(2') -C(22')	112.64(19)
N(2) - N(3) - C(4)	124.04(16)	C(1') -C(2') -C(23')	107.45(19)
N(3) - C(4) - C(5)	123.45(17)	C(21') -C(2') -C(22')	110.10(20)
N(3) - C(4) -C(1')	111.35(15)	C(21') -C(2') -C(23')	108.79(20)
C(5) - C(4) -C(1')	124.05(17)	C(22') -C(2') -C(23')	109.60(21)
C(4) - C(5) -C(5a)	126.09(17)	C(1') -O(1') -C(3')	117.03(15)
C(5) -C(5a) - C(6)	119.73(17)	O(1') -C(3') -O(3')	122.26(19)
C(5) -C(5a) -C(9a)	121.46(16)	O(1') -C(3') -C(1P)	112.82(17)
C(6) -C(5a) -C(9a)	118.81(17)	O(3') -C(3') -C(1P)	124.92(19)
C(5a) - C(6) - C(7)	121.02(19)	C(3') -C(1P) -C(2P)	122.41(18)
C(6) - C(7) - C(8)	120.12(20)	C(3') -C(1P) -C(6P)	117.94(19)
C(7) - C(8) - C(9)	119.93(20)	C(2P) -C(1P) -C(6P)	119.65(20)
C(8) - C(9) -C(9a)	120.67(19)	C(1P) -C(2P) -C(3P)	120.01(21)
C(1) -C(9a) -C(5a)	117.05(16)	C(2P) -C(3P) -C(4P)	119.80(24)
C(1) -C(9a) - C(9)	123.55(17)	C(3P) -C(4P) -C(5P)	120.3(3)
C(5a) -C(9a) - C(9)	119.38(17)	C(4P) -C(5P) -C(6P)	120.5(3)
C(4) -C(1') -C(2')	117.87(17)	C(1P) -C(6P) -C(5P)	119.76(23)
C(1M) - C(1) - N(2) - N(3)	-156.46(18)	C(7) - C(8) - C(9) -C(9a)	-0.2(3)
C(9a) - C(1) - N(2) - N(3)	79.09(20)	C(8) - C(9) -C(9a) - C(1)	176.96(19)
C(1M) - C(1) -C(9a) -C(5a)	169.87(18)	C(8) - C(9) -C(9a) -C(5a)	-2.0(3)
C(1M) - C(1) -C(9a) - C(9)	-9.1(3)	C(4) -C(1') -C(2') -C(21')	-57.33(24)
N(2) - C(1) -C(9a) -C(5a)	-71.00(20)	C(4) -C(1') -C(2') -C(22')	64.59(25)
N(2) - C(1) -C(9a) - C(9)	110.02(20)	C(4) -C(1') -C(2') -C(23')	-174.61(19)
C(1) - N(2) - N(3) - C(4)	-7.7(3)	O(1') -C(1') -C(2') -C(21')	-179.97(17)
N(2) - N(3) - C(4) - C(5)	-46.3(3)	O(1') -C(1') -C(2') -C(22')	-58.08(22)
N(2) - N(3) - C(4) -C(1')	145.53(18)	O(1') -C(1') -C(2') -C(23')	62.72(22)
N(3) - C(4) - C(5) -C(5a)	13.8(3)	C(4) -C(1') -O(1') -C(3')	77.27(19)
C(1') - C(4) - C(5) -C(5a)	-179.60(17)	C(2') -C(1') -O(1') -C(3')	-154.62(17)
N(3) - C(4) -C(1') -C(2')	92.06(20)	C(1') -O(1') -C(3') -O(3')	-5.5(3)
N(3) - C(4) -C(1') -O(1')	-146.52(15)	C(1') -O(1') -C(3') -C(1P)	173.96(16)
C(5) - C(4) -C(1') -C(2')	-75.99(25)	O(1') -C(3') -C(1P) -C(2P)	2.4(3)
C(5) - C(4) -C(1') -O(1')	45.43(24)	O(1') -C(3') -C(1P) -C(6P)	-177.79(19)
C(4) - C(5) -C(5a) - C(6)	-151.04(19)	O(3') -C(3') -C(1P) -C(2P)	-178.12(21)
C(4) - C(5) -C(5a) -C(9a)	29.5(3)	O(3') -C(3') -C(1P) -C(6P)	1.7(3)
C(5) -C(5a) - C(6) - C(7)	178.14(19)	C(3') -C(1P) -C(2P) -C(3P)	178.24(21)
C(9a) -C(5a) - C(6) - C(7)	-2.4(3)	C(6P) -C(1P) -C(2P) -C(3P)	-1.6(3)
C(5) -C(5a) -C(9a) - C(1)	3.6(3)	C(3') -C(1P) -C(6P) -C(5P)	-179.20(22)
C(5) -C(5a) -C(9a) - C(9)	-177.33(18)	C(2P) -C(1P) -C(6P) -C(5P)	0.6(3)
C(6) -C(5a) -C(9a) - C(1)	-175.77(17)	C(1P) -C(2P) -C(3P) -C(4P)	1.4(4)
C(6) -C(5a) -C(9a) - C(9)	3.3(3)	C(2P) -C(3P) -C(4P) -C(5P)	-0.2(4)
C(5a) - C(6) - C(7) - C(8)	0.3(3)	C(3P) -C(4P) -C(5P) -C(6P)	-0.7(4)
C(6) - C(7) - C(8) - C(9)	1.1(3)	C(4P) -C(5P) -C(6P) -C(1P)	0.5(4)

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ASYMMETRIC INDUCTION IN THE 1,7 RING CLOSURE OF DIENE-CONJUGATED
 DIAZO-COMPOUNDS: A ROUTE TO CHIRAL 1H-2,3-BENZODIAZEPINES

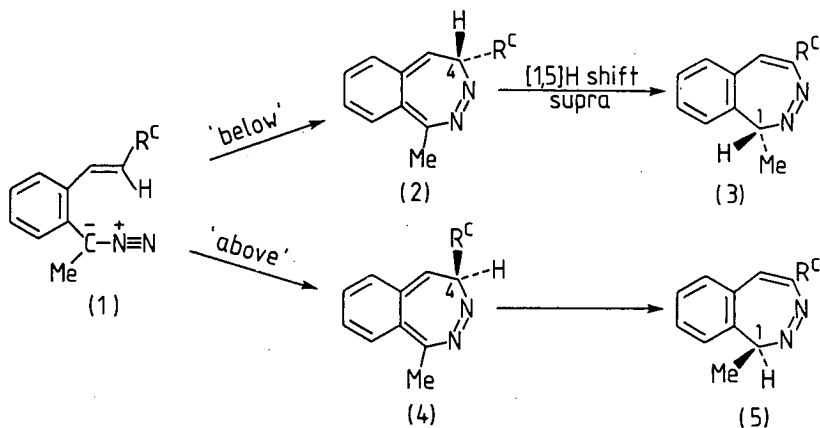
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In the cyclisation of the diazo-compound (7) to give the diastereomeric pair of 1H-2,3-benzodiazepines (8) and (9), alkoxy groups, when present as the medium sized group M, show the opposite effect in promoting face selectivity to that of alkyl groups and the alkoxide ion. Thus when M=OMe the (8):(9) ratio is 92:8 while in contrast when M=O⁻ the ratio is 15:85.

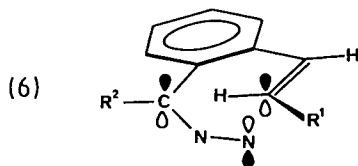
Studies on asymmetric induction have embraced many types of reaction since Cram's original work on nucleophilic addition to the carbonyl group. In particular there has been extensive work on the addition reactions of alkenes, both via electrophilic attack and via cycloaddition.^{1,2,3} We now report the first study of asymmetric induction in the electrocyclisation reactions of conjugated 1,3-dipolar intermediates. Such reactions provide powerful synthetic routes to both 5- and 7-membered heterocyclic rings; the former by the 1,5 electrocyclisation of alkene-conjugated 1,3-dipoles,⁴ and the latter by the 1,7 closure of diene-conjugated analogues.⁵

The reaction chosen for this study was the cyclisation of diazo-compounds of the type (1) to give 1H-2,3-benzodiazepines (Scheme 1).

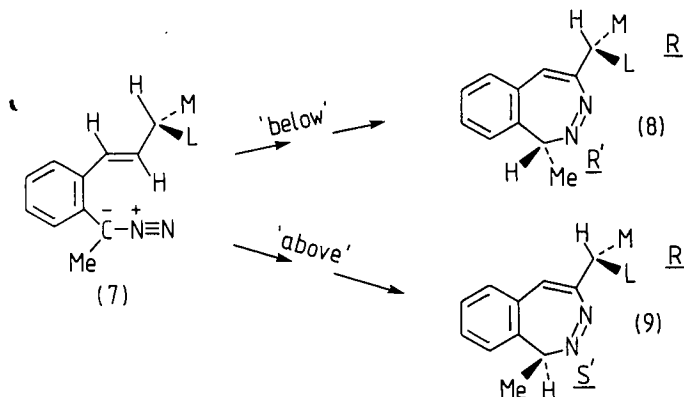


Scheme 1

It is thought that this conversion involves two steps, first a 1,7-electrocyclisation (8π electron) in which orbital overlap at the termini of the π system is achieved via a helical transition state (6); and second, an intramolecular sigmatropic [1,5] hydrogen shift (suprafacial) which converts, for example, (2) into (3).^{6,7}



The results reported here are concerned with the effect on the course of the reaction of the presence of a chiral substituent R^C in the *trans* position at the olefinic terminus of the conjugated system (Scheme 1). Cyclisation of (1) can occur via approach of the terminal nitrogen to either face of the double bond, so producing as the primary products a pair of diastereomers (2) and (4) which have a new chiral centre at C-4 adjacent to R^C . The suprafacial hydrogen migration in the second step will then transfer the chirality at C-4 stereospecifically to C-1 to produce the product pair of diastereomers (3) and (5) which have the new chiral centre remote from the original stereogenic group.



Scheme 2

The primary objective in this work was to vary the nature of R^C to determine the factors controlling stereoselectivity in the cyclisation step. We have looked at the cyclisation of compounds of the type (7) in which the largest group (L) is Ph or Bu^t ; the medium sized group (M) is alkyl (Me or Et), alkoxy (OMe or $OSiMe_2Bu^t$), or alkoxide ion (O^-); and the smallest group is hydrogen. The cyclisations^{6,7} were carried out at ca 80°C in aprotic solvents of various kinds (Table). The ratios of the diastereomers (8):(9) were measured by 1H NMR and by HPLC on the crude reaction products before crystallisation or chromatography, and the relative configurations of the two chiral centres were determined by X-ray crystallography (cases a, b, d, e) or by comparison of NMR spectra.

Table yields and diastereomer ratios for the products from Scheme 2

(7)			(8):(9)		
M	L	total yield %	CX	reaction DME	solvent* DMF
(a)	Me	Ph	70	55:45	-
(b)	Me	Bu ^t	85	58:42	55:45
(c)	Et	Bu ^t	86	63:37	62:38
(d)	OMe	Ph	80	44:56	-
(e)	OMe	Bu ^t	85	8:92	10:90
(f)	OSiMe ₂ Bu ^t	Bu ^t	92	9:91	-
(g)	O ⁻	Bu ^t		85:15	-

* CX=cyclohexane, DME=1,2-dimethoxyethane, DMF=N,N-dimethylformamide

The results are shown in the Table. All cyclisations were carried out using racemates, but for illustration the results are presented and discussed for the enantiomer shown in structure (7). In the products (8) and (9) this is the *R* configuration of R^C for all the cases in the Table. The configuration of the new chiral centre at C-1 is given as R' or S'.

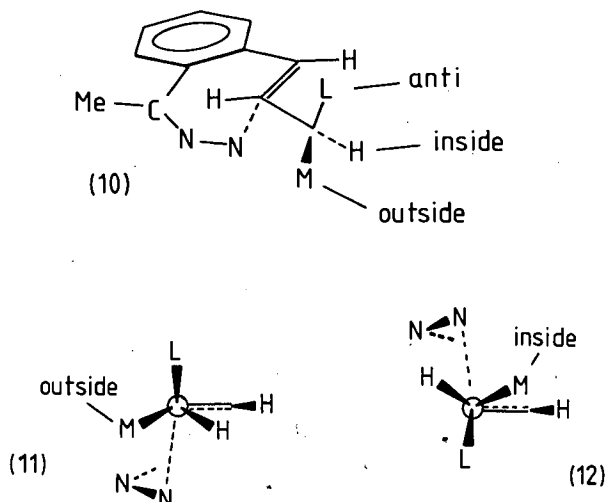
The most striking observation is that alkyl groups and the alkoxide ion, when present as the medium sized group M, have the opposite effect to that of alkoxy groups in inducing face selectivity. Thus (8) is the major product when M=Me or Et (cases a, b, c), and when M=O⁻ (case g); but (9) is favoured when M=OMe or OSiMe₂Bu^t (cases d, e, f). In the discussion following we make the assumption, based on Houk's earlier work on cycloaddition reactions, that in the transition states leading to both diastereomers the largest group L is in the position *anti* to the attacking N. This is illustrated in (10) and in the partial structures (11) and (12) which, respectively, represent attack from 'below' and 'above' the plane of the double bond.

In the cases where M is an alkoxy group, cyclisation at the 'upper' face predominates via the transition state (12) which has the alkoxy group in the 'inside' position. This 'inside' preference of alkoxy groups can be strong (cases e, f) giving a ratio of diastereomers of >90:10. In contrast there is a remarkable reversal of face selectivity when M=O⁻. The cyclisation then shows a strong preference (85:15) for attack at the 'lower' face via (11). Alkyl groups show the same effect but to a much lesser degree. The transition state (11) has the O⁻ or alkyl group in the 'outside' position.

These results make an interesting comparison with those of Houk and others on the cycloaddition reactions of nitrile oxides to alkenes.^{1,2,3} In these reactions alkyl and alkoxy groups both occupy the 'inside' position in the favoured transition state. The effect of having M=O⁻ was not examined but hydroxyl groups showed a moderate 'outside' preference.

Further work is needed before a firm rationalisation of these

observations can be advanced. The facial selectivity obviously depends on the chemical nature of the medium sized group and not simply on its size. It must therefore arise from a combination of steric and stereoelectronic



effects. The 'inside alkoxy' effect in cycloadditions has been attributed both to polar repulsion and to a stereoelectronic effect related to its interaction with the π -system. In the latter explanation Houk has pointed out that this 'inside' position, close to the molecular plane of the alkene moiety, minimises electron withdrawal from the π bond via σ_{C-O}^*/π overlap.^{1,2} In these diene-conjugated diazo compounds this position would be favoured since the π system is already electron deficient because of the electron withdrawing diazo group and any further electron withdrawal at the other end of the π system would be destabilising. If that is so then it may be that the 'outside' position for O^- and the alkyl groups is the one which best allows them to donate electrons into the π -system.

Whatever the explanation it is clear that the 'inside alkoxy' effect and the 'outside alkoxy' effect manifested here give a degree of control of selectivity which is high enough to be potentially useful in the synthesis of chiral benzodiazepines. Similar studies on the cyclisation of other 1,3-dipolar intermediates are in progress.

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